14 Hematopoietic cell transplantation and cellular therapy

Irum Khan, Nirav N. Shah, and Matthew Ulrickson

History 381
Clinical transplantation of hematopoietic progenitor cells 382
Hematopoietic progenitor cell mobilization and procurement 382
Allogeneic transplantation 383
Cell source 385
Additional donor features 385
Adoptive cell therapy 386
The hematopoietic cell transplantation process 389
Hematopoietic cell transplantation complications 394
Specific organ toxicities 396
CAR T–related complications 399
Late effects 401
Disease-specific indications for HCT and cellular therapy 403
Nonmalignant hematologic diseases 410
Solid tumors 412
Health inequities in transplantation 412
Economics of hematopoietic cell transplantation 413
Summary 413
Bibliography 413

The online version of this chapter contains an educational multimedia component on CAR T-cell therapy.

History

The advent of the atomic era in the 1940s and the potential for large-scale human exposure to ionizing radiation increased research in hematopoiesis and hematopoietic cell transplantation (HCT) as a therapeutic strategy against exposure to lethal radiation. The following influential observations were required to develop the field: (1) safety and feasibility of human bone marrow infusion, (2) ability of normal stem cells to reconstitute a lethally radiated host, (3) recognition of a potential graft-versus-tumor (GVT) effect operative in animal models and humans, and (4) safety and feasibility of cryopreserved autologous bone marrow in reconstituting lethally radiated hosts

The initial clinical experience with HCT was dismal, with almost all patients dying from transplant-related complications, the notable exception being patients who received a hematopoietic graft from an identical twin. It was not until the discovery and identification of human leukocyte antigens (HLAs), as well as improvements in supportive care with antibiotics and antifungals, that HCT warranted large-scale study. A landmark paper from Thomas et al, demonstrating that long-term remission could be achieved in patients with refractory acute leukemia following high-dose chemoradiotherapy and infusion of HLA-identical sibling bone marrow, marked the beginning of clinical HCT.

The rationale for high-dose cytotoxic chemotherapy stems from the steep dose-response curve of alkylating agents and radiotherapy. Doubling the dose of alkylating agents increases tumor cell kill by a log or more and increasing the dose of alkylating agents by 5- to 10-fold overcomes the resistance of most tumor cells. In 1978, investigators from the National Cancer Institute were the first to report the use of high-dose chemotherapy followed by autologous HCT

Conflict-of-interest disclosure: Irum Khan: honoraria: Takeda, Celgene. Nirav N. Shah: honoraria/travel support: Incyte, Celgene, Lily, Miltenyi Biotech; advisory board: Lily, Kite, Celgene, Legend, Epizyme, Seattle Genetics, TG Therapeutics; equity ownership: Exelixis, Geron; research support: Miltenyi Biotec. Matthew Ulrickson: no competing financial interests to declare.

Off-label drug use: Irum Khan, Nirav N. Shah, Matthew Ulrickson: drug and cellular therapy for hematologic malignancies and hematopoietic cell transplantation.

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavrilaki on 10 December 2022

for patients with relapsed lymphoma. These encouraging results were the initial clinical evidence leading to the widespread application of autologous HCT. McElwain and Powles demonstrated a similar dose-response curve for melphalan in patients with myeloma, which led to the beginning of high-dose therapy for myeloma, the most common indication for autologous HCT.

High-dose chemotherapy led to significant toxicity, however, and limited the ability of patients with comorbidities or older age to access this potentially curative therapy. This led to the development of reduced-intensity conditioning (RIC) for allogeneic transplantation, where lower doses of chemotherapy and radiation effectively enabled engraftment and GVT effect in less fit patients. Additionally, the requirement for an HLA-matched sibling or unrelated donor also limited access to HCT, leading to expansion of donor options including mismatched unrelated donors, umbilical cord blood (UCB) units, and later haploidentical transplantation. These advancements significantly improved the ability of populations underrepresented in the unrelated donor pool to access HCT.

Even with these advances in the field, graft-versus-host GVHD disease remains a significant contributor to morbidity and mortality in patients treated with HCT. This challenge has contributed to the development of cellular therapies aimed to enable GVT without any risk of GVHD. The most notable example is chimeric antigen receptor (CAR) T cells, where curative potential has been demonstrated following cell infusion without risk of GVHD.

Clinical transplantation of hematopoietic progenitor cells

HCT traditionally has been classified according to the source of hematopoietic progenitor cells (HPCs) as either autologous or allogeneic. Allogeneic donors may be matched sibling (related), matched unrelated, mismatched unrelated, haploidentical (relative sharing 1 HLA haplotype), or unrelated newborns via umbilical cord blood. In addition, hematopoietic cells for transplantation may come from either harvested bone marrow, mobilized peripheral blood, or cord blood.

Autologous transplantation

Autologous HCT uses HPCs obtained from the patient, who is both the donor and the recipient of these cells. Concurrent with the observation that 2/3 of resistant myeloma patients evidenced remarkable antitumor activity after a single dose of melphalan 3 to 4 times higher than the standard dose, severe and prolonged bone marrow depression caused the death of about 1/3 of treated patients. This complication can usually be prevented by infusion of autologous bone marrow after completion of high-dose chemotherapy, which reduced the duration and toxicity of severe myelosuppression. Later, Granulocyte-Colony Stimulating Factor (G-CSF)–mobilized peripheral blood HPCs were shown to prevent prolonged myelosuppression and remain the predominant cell source for autologous transplantation. Autologous HCT is most effective when there is direct correlation between chemotherapy dose and tumor response and when the dose-limiting treatment toxicity for the chemotherapeutic is myelosuppression. For a review of the indications for autologous transplant in specific diseases, please see the applicable sections later in this chapter.

Hematopoietic progenitor cell mobilization and procurement

HPCs reside primarily in the bone marrow but circulate at low levels in the peripheral blood. Chemotherapy, G-CSF, and the CXCR4 inhibitor plerixafor can mobilize large quantities of HPCs into the peripheral blood for subsequent collection via leukapheresis. With the advent of the cryopreservation agent dimethyl sulfoxide, cryopreservation of peripheral blood (or marrow) HPCs became feasible and was rapidly adopted for autologous HPCs.

Various strategies have been developed to mobilize HPCs into the bloodstream. This includes single-agent cytokine (typically G-CSF), and combinations of chemotherapy with cytokines followed by collection of peripheral blood leukocytes with leukapheresis. HPC concentration in the bloodstream usually peaks 4 to 6 days after initiation of therapy with G-CSF. When chemotherapy with G-CSF is given, maximum recovery of HPCs in the blood occurs at the time of marrow recovery and usually leads to higher cell yields than growth factor alone. Collection is usually initiated when the white blood cell (WBC) count recovers to $>2 \times 10^9$ WBC/L. and peripheral blood CD34+ cell content exceeds 10 cells/μL. Identification of patients with suboptimal preapheresis Peripheral Blood (PB) CD34+ counts allows for the salvage of mobilization attempts, thereby reducing failure rates.

Mobilized peripheral blood HPCs have almost completely replaced bone marrow as the HPC source for patients undergoing autologous HCT because of the less invasive collection method and more rapid blood count recovery after reinfusion. In the autograft, increasing cell dose is associated with more rapid platelet and neutrophil recovery when stem cell doses of at least 2 million CD34+ cells/kg are used. CD34+ cell doses lower than 2 million CD34+ cells/kg compromise the efficiency and success of engraftment and doses lower than 2.5 million CD34+

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022

cells/kg delay platelet engraftment. Higher CD34+ cell doses >5 × 10^6/kg do not have meaningful clinical benefit in the autologous setting.

Despite the use of chemotherapy-cytokine combination regimens, mobilization failure still occurs in some patients needing an autologous HCT. Prior chemotherapy and/or radiation treatment is the most important factor affecting stem cell yields. Prior treatment with lenalidomide and purine analogs, recent chemotherapy, previous radiation, hypocellular marrow at collection, clonal hematopoiesis of indeterminate potential, malignancies involving the bone marrow, premobilization thrombocytopenia, and refractory disease are associated with poor mobilization. This underscores the importance of referring a potential transplantation candidate early for autologous transplantation evaluation before repeated salvage chemotherapy attempts adversely affect stem cell collections.

A small-molecule CXCR4 inhibitor, plerixafor, in combination with G-CSF, can help overcome failure to mobilize in some patients. Plerixafor is an antagonist of CXCR4 and prevents interaction with stromal cell-derived factor-1 (SDF-1). Plerixafor causes a rapid and significant increase in the total WBC and peripheral blood CD34+ counts 4 to 9 hours after a single injection. In 2 phase 3 randomized studies comparing G-CSF alone or G-CSF with plerixafor, a significantly higher proportion of patients in the G-CSF–plerixafor arm collected adequate stem cells compared with the G-CSF alone arm. The most common adverse events associated with plerixafor include diarrhea and injection site reactions.

HPC modifications

After collection of autologous HPCs, there is significant opportunity for cell modifications that have potential use in the treatment of diseases affecting the hematopoietic system. One of the most successful to date involves the use of clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 gene editing of HPCs ex vivo followed by reinfusion of the modified product. While still in early phase studies, this has shown potential benefit in patients with sickle cell disease, β-thalassemia, and may be applicable in patients with HIV as well.

Allogeneic transplantation

Alloreactivity in the treatment of hematologic malignancies

In allogeneic HCT, the conditioning regimen eradicates malignant cells, ineffective hematopoietic cells in the case of nonmalignant disorders, and host immune cells that may reject the donor cells. Although HCT was originally regarded as a way of rescuing patients from therapy-induced marrow aplasia, it is now accepted that alloreactive donor cells produce a substantial GVT effect that contributes to long-term cancer control.

The importance of GVT was initially studied by comparing relapse rates between syngeneic (identical twin donor) and allogeneic HCT recipients, considering the relation between graft-versus-host disease (GVHD) and relapse, and examining the effect of T-cell depletion of the graft on risk of disease recurrence. Patients with acute myeloid leukemia (AML) in first complete remission (CR1) and chronic myelogenous leukemia (CML) in chronic phase had an increased rate of recurrence after syngeneic HCT relative to allogeneic HCT. In addition, patients with graft-versus-host disease were noted to have a lower risk of relapse compared to patients without GVHD.

Allogeneic hematopoietic cell transplantation and human leukocyte antigen typing

Allogeneic HCT uses HPCs obtained from a related or unrelated donor. The ideal allogeneic donor is identified according to HLA compatibility. The major histocompatibility complex (MHC) refers to the entire genetic region containing the genes encoding tissue HLA antigens. In humans, the MHC region lies on the short arm of chromosome 6. The HLA region is a relatively large section of chromosome 6 with many genes, divided into class I, class II, and class III regions, each containing numerous loci that encode a large number of polymorphic alleles.

The class I HLA antigens, HLA-A, -B, and -C, are expressed on almost all cells of the body at varying densities. The class II antigens include DR, DQ, and DP antigens, are expressed on B cells and monocytes, and are induced on many other cell types following inflammation or injury.

Determination of HLA types has refined as typing has become molecularly based, replacing earlier serologic or cellular techniques. Modern HLA typing relies on polymerase chain reaction (PCR) amplification followed by probing with labeled short sequence-specific oligonucleotide probes or sequencing of the MHC class I and class II alleles. By convention, differences recognized by serologic typing are called antigen mismatches, and differences recognized only by molecular techniques are called allele mismatches. In addition to the HLA genes, a large number of other genes encoding cell surface proteins are collectively termed *minor histocompatibility antigens*. As individual proteins, they play a more modest role in an alloimmune response but are collectively likely to direct both GVHD

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022

and graft-versus-tumor responses. Detailed guidelines exist to inform donor choice based on molecular typing (https://bethematchclinical.org/).

Donor selection

A complete HLA-matched related donor (MRD) is usually the first choice of allogeneic donor. MRD cells cause less GVHD, less morbidity and mortality, and are easier to coordinate for timing of transplantation. Sibling pairs have a ~25% chance of being HLA-identical. Crossover phenomena during meiosis explain rare cases of aberrant recombination of HLA antigens resulting in a probability slightly lower than 25%.

Given diminishing family sizes and the increasing age of recipients, medically fit sibling donors are often not available. Thus, many allogeneic transplants rely on matched unrelated donors (MUDs), matched at HLA-A, -B, C, DRB1, and DQB1 loci (10/10). In linkage disequilibrium, alleles occur together with a greater frequency than would be expected by chance and is more frequently observed between loci that are in close proximity (eg, between HLA-B and -C and HLA-DRB1 and -DQB1). Millions of potential donors have been HLA typed and are listed in national and international registries. Thus, for patients with common HLA types, it is now possible to find donors on a routine basis. It is more difficult, however, to find a donor for patients with infrequent haplotypes or for patients with polymorphic HLA backgrounds. Despite matching for HLAs, unrelated donors are much more likely to be a mismatch at minor histocompatibility antigens.

Alternative donor transplantation: umbilical cord blood and haploidentical grafts

Because of the inability to identify a matched related or unrelated donor for all patients in need of an allogeneic HCT, additional sources of HPCs have been explored. It is estimated that a quarter to a third of patients in need of transplant are not able to find a standard match. Umbilical cord blood cells represent an alternative source of HPCs. UCB contains HPCs capable of hematopoietic reconstitution and less allogeneic reactivity responsible for GVHD compared to marrow or peripheral blood grafts. Because of the relative immaturity of the newborn immune system, cord blood transplantation can be performed with a relatively low incidence of GVHD even with 2 and 3 HLA antigen mismatches.

The greatest limitations of UCB transplantation are slow engraftment with prolonged cytopenias (median Absolute Neutrophil Count recovery 3 to 4 weeks), engraftment failure rates up to 10%, and delayed immune reconstitution that results in higher rates of death from infection. These limitations correlate with progenitor cell dose in cord blood units and suggest the need for selection of cord units with a higher cell dose per kg of recipient weight. The most used definition of "adequate" cell dose is $\geq 2.5 \times 10^7$ nucleated cells/kg, with higher doses preferred in the setting of greater HLA mismatch. When UCB units lack the requisite number of progenitor cells, the use of 2 UCB units enables a higher cell dose. Two randomized controlled trials in children and young adults compared transplantation using 2 UCB units versus a single UCB unit and concluded that single UCB transplantation with adequate cell dose is preferable to 2 UCB units unless a single unit of adequate cell dose is not available.

Another potential source of stem cells for patients without an HLA-matched donor is haploidentical family members sharing 1 HLA haplotype. Parents and their children are HLA haploidentical with each other and siblings have a 50% chance of being haploidentical with each other. It is estimated that approximately 90% of patients have a haploidentical donor. Because of the mismatch, without additional intervention, haploidentical transplant would be associated with unacceptable rates of graft failure and severe GVHD. The predominant strategy to ameliorate these limitations is through immunomodulation of the T-cell replete graft by functionally impairing alloreactive T cells with the use of posttransplant cyclophosphamide (PT-Cy) given on days +3 and +4. Early after transplant, alloreactive effector T cells are more susceptible to alkylator therapy because of their rapid proliferation, while hematopoietic stem cells and nonalloreactive regulatory T cells are relatively spared because of their quiescence. In addition, expression levels of aldehyde dehydrogenase, which metabolizes cyclophosphamide to an inactive metabolite, are higher in $CD4^+Foxp3^+$ regulatory T cells and contributes to a relative sparing and faster recovery of this population and further immunomodulation of the graft. This therapy enables rates of GVHD comparable to, and potentially lower, than that seen with MRD and MUD donors and has led to investigation into whether this represents an optimal method for GVHD prophylaxis in all donor types as part of Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 1703. Retrospective comparisons have shown similar results for recipients of haploidentical and Unrelated Donor transplants. The presence of clinically significant donor-specific antibodies (DSAs) in the recipient, directed against donor HLA, has been reported to induce graft failure in up to 75% of haploidentical recipients and these donors should be avoided or used after treating the recipient to lower DSA titers.

To clarify the optimal choice of alternative donor, the BMT CTN 1101 study randomized patients to

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022

haploidentical versus double UCB transplant for the treatment of leukemia or lymphoma. Reduced-intensity conditioning (Flu/Cy/TBI) was used and while the 2-year progression-free survival (PFS) was similar within the 2 groups, 2-year overall survival was higher (57% versus 46%, $P = 0.04$) and nonrelapse mortality (NRM) lower (11% versus 18%, $P = 0.04$) with a haploidentical source, suggesting it is the preferable alternative donor source.

Cell source

Bone marrow versus mobilized peripheral blood

Since the 1990s, peripheral blood HPCs (PB-HPCs) have steadily surpassed Bone Marrow (BM) as an HPC source because of faster engraftment, donor preference, and feasibility. The Center for International Blood and Marrow Transplant Research (CIBMTR) reported that between 2007 and 2011 about 70% to 80% of adult allogeneic transplant recipients received Peripheral Blood Stem cells (PBMCs).

A systematic review, which included 9 randomized controlled trials and 1521 related and unrelated donor allogeneic BMT recipients with hematologic malignancies, demonstrated that overall survival and disease-free survival between the 2 graft sources were comparable. PBSC led to faster neutrophil and platelet engraftment and a significant increase in grade 3 to 4 acute GVHD and extensive chronic GVHD at 3 years. PBSC was associated with a decrease in relapse (21% versus 27% at 3 years) both for advanced and early stage hematologic malignancies. However the role of BM as a preferred source was strengthened by the BMT CTN 0201 randomized trial demonstrating that patients undergoing MUD transplant with myeloablative conditioning (MAC) and GVHD prophylaxis using methotrexate and calcineurin inhibitors with a PB-HPC graft experienced more chronic GVHD than those who received BM-HPC (53% versus 41%, $P = 0.01$). There was no difference in relapse, disease-free survival, or overall survival between the 2 treatment arms; although BM-HPC recipients had a higher incidence of graft failure (9% versus 3%, $P = 0.02$). In addition, BM-HPC recipients reported better psychological well-being, less burdensome chronic GVHD symptoms and were more likely to return to work at 5 years after BMT. However, donor preference (30% of screened donors declined randomization in the CTN trial), as well as additional options for prophylaxis of GVHD such as PT-Cy, makes the adoption of BM over PBSC an uncommon practice at most transplant centers. One notable exception is the predominant use of BM-HPCs for patients undergoing transplant for severe aplastic anemia. Without a significant need for GVT effect, decreasing the risk of GVHD is even more impactful and BM demonstrates improved survival in all age groups when compared with PBSC, largely through reduction in rates of acute and chronic GVHD.

Additional donor features

Age

Studies examining the effect of donor age on transplant success show that younger donors result in better outcomes for patients, resulting in a donor age limit of 60 years in the National Marrow Donor Program registry; most registry participants selected to be donors are between the ages of 18 and 35-years-old. In fact, donor age is the only non-HLA related donor feature shown to date that affects survival in allogeneic transplant.

Donor-specific antibodies

Allogeneic hematopoietic stem cell recipients may have preformed antibodies directed against foreign HLA antigens. The use of partially HLA-mismatched allogeneic HPC donors allows for the possibility of the presence of circulating HLA DSAs in the recipient. Anti-HLA antibodies against mismatched HLA antigens increase graft failure. Common exposures contributing to DSAs include pregnancy, blood product transfusion, and previous organ or blood transplantation. DSAs tend to be of higher intensity when directed against haploidentical first-degree relatives. DSA assessment requires frequent monitoring because their relative strength can change over time. Although the criteria that constitute a prohibitive DSA are unknown, therapies that decrease antibody levels can result in more successful engraftment.

Killer immunoglobin-like receptor ligand

Natural killer (NK) cells are a critical component of innate immunity, modifying T-cell alloreactivity, and are among the earliest lymphocyte subsets to reconstitute and achieve functional maturity (within weeks) after HCT. Killer immunoglobulin-like receptors (KIRs) control NK function and are encoded by the highly polymorphic *KIR* gene family.

In patients with AML who undergo HCT, lack of HLA ligand for donor KIR (KIR mismatch) was associated with superior NK reactivity and lower relapse in an initial study because of lack of NK inhibition, termed *KIR better*. A study of 1328 patients with AML who received HLA-compatible allografts, donor-recipient *KIR3DL1*/HLA-B subtype combinations with weak or no inhibition in vitro were associated with significantly lower relapse and higher survival than strong inhibition combinations.

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022

Since this study, others have not confirmed this impact of relapse, leading to growing evidence that KIR plays a more significant role in the setting of reduced-intensity conditioning and in the setting of the donor KIR B haplotype. Refining donor selection algorithms to include *KIR3DL1*/HLA-B subtype analysis to avoid strong inhibition donors may reduce relapse and improve survival.

Donor ABO and cytomegalovirus status

After selection of the optimal donor based on HLA match, other considerations include ABO and cytomegalovirus (CMV) status of the donor and recipient pair, though, importantly, these do not have the same impact on survival as do HLA-mismatches. CMV-seropositive recipients have the highest risk of CMV reactivation, followed by seronegative recipients who receive HPCs from a CMV-seropositive donor so, when possible, selection of CMV seronegative donors is preferred for CMV seronegative recipients. Similarly, while allogeneic transplants can be performed in ABO-mismatches, an ABO match is preferable to reduce red blood cell transfusion requirements and risk for hemolysis. Table 14-1 lists the major, minor, and bidirectional mismatches that occur with various donor and recipient pairing.

Graft manipulation

The possibility of separating risk of GVHD from likelihood of GVT continues to be eagerly pursued, both through manipulation of the graft as well as through adoptive cellular therapy. T cells are the major component exerting an adaptive or innate immune response. Graft manipulation usually involves depletion of T cells that are implicated in GVHD. Methods of ex vivo T-cell depletion include negative selection of T cells, which can be performed with antibodies, or an alternative strategy of CD34-positive selection using immunomagnetic beads. A CD34-selected graft was compared with tacrolimus/methotrexate after a BM graft in the BMT CTN 1301 study investigating calcineurin inhibitor-free regimens for GVHD prophylaxis in patients 65 years or older with an HLA-matched donor. This study showed a chronic GVHD rate of 60.2% in the CD34-selected graft compared to 56.6% in the control group ($P = 0.23$) though overall survival at 1 year was 75.7% in the CD34 group compared to 84.2% in the control group ($P = 0.02$ and HR 1.74). As shown in this study, while aggressive T-cell depletion reduces the risk of acute and chronic GVHD, it comes at the cost of increased risk of relapse, graft failure, and infection, and this has hindered widespread adoption.

Table 14-1 ABO matching in HCT

	Recipient ABO group	Donor ABO group
Major mismatch	O	A B AB
	A	AB
	B	AB
Minor mismatch	A	O
	B	O
	AB	A B O
Bidirectional match	A	B
	B	A

HCT, hematopoietic cell transplantation.

Adoptive cell therapy

Adoptive cell therapy is the transfer of autologous or allogeneic immune cells with direct activity against cancers or infections into a patient. The approach dates back to the late 1980s when ex vivo expanded autologous populations of tumor-infiltrating lymphocytes (TILs) mediated tumor regression in patients with metastatic melanoma. Over the past 2 decades, advances in gene-transfer technologies have enabled efficient redirection of immune cells toward cancer antigens to overcome immune tolerance seen with tumor-infiltrating lymphocytes. To date, most of the progress in adoptive cell therapy has been in hematologic malignancies with engineered T cells expressing CARs, with multiple CD19-directed therapies (tisagenlecleucel, axicabtagene ciloleucel, brexucabtagene autoleucel, and lisocabtagene maraleucel), now United States Food and Drug Administration (FDA)-approved, and 1 multiple myeloma [MM] CAR T-cell product (idecabtagene vicleucel) also approved with several other CAR T-cell products on the horizon. Emerging data also support efficacy of T cells with engineered T-cell receptors (TCRs) as well as adoptively transferred NK cells. Adoptive cell therapy is also being studied for the treatment of opportunistic infections in immunocompromised patients.

Cancer therapy with chimeric antigen receptor–modified T cells

Adoptive cell therapy with T cells genetically engineered to express a CAR has emerged as a treatment modality for patients with hematological malignancies. In its basic (first-generation) form, a CAR is a recombinant receptor construct consisting of an extracellular single-chain variable fragment of an antibody recognizing a tumor-associated cell surface antigen, a spacer

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022

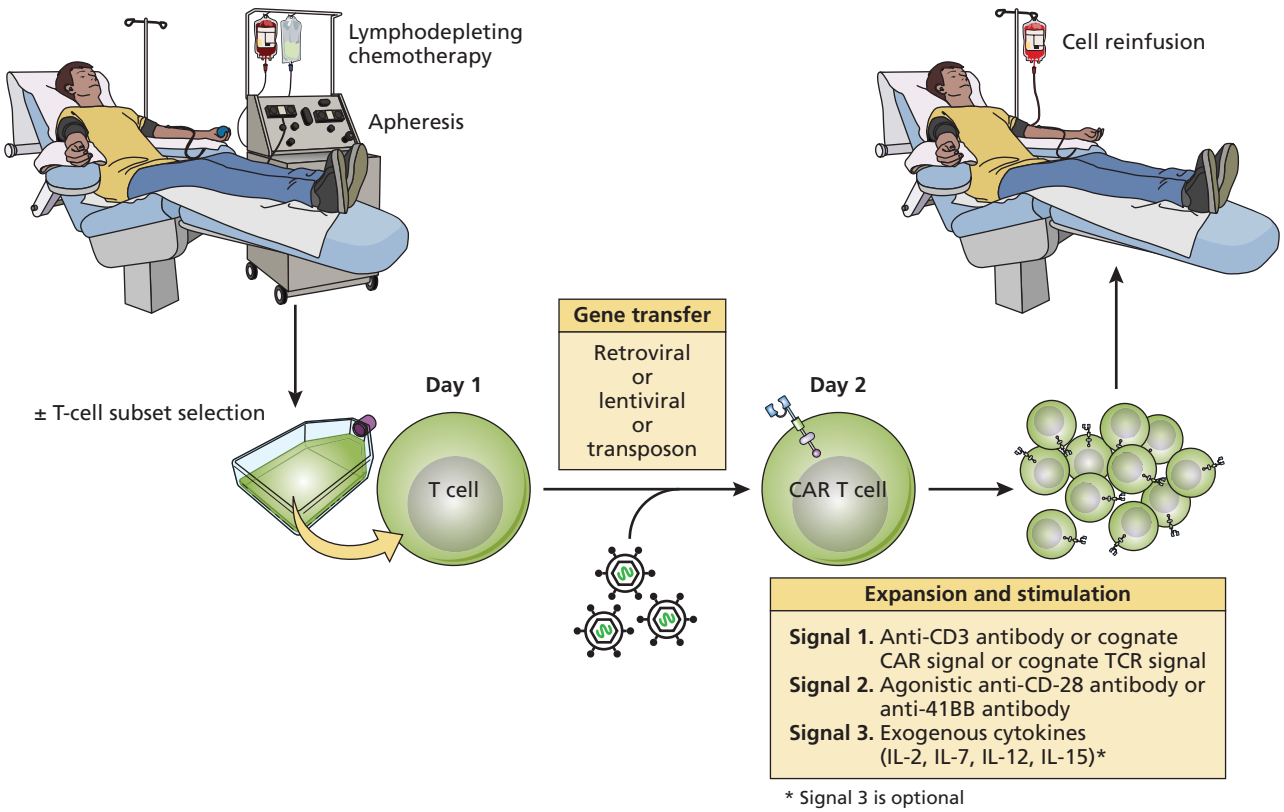
Lymphodepleting chemotherapy
Apheresis
Cell reinfusion
± T-cell subset selection
Day 1
Gene transfer
Retroviral or lentiviral or transposon
Day 2
T cell
CAR T cell
Expansion and stimulation
Signal 1. Anti-CD3 antibody or cognate CAR signal or cognate TCR signal
Signal 2. Agonistic anti-CD-28 antibody or anti-41BB antibody
Signal 3. Exogenous cytokines (IL-2, IL-7, IL-12, IL-15)*
* Signal 3 is optional

Figure 14-1 The process to generate chimeric antigen receptor (CAR)-modified T cells. Patients undergo steady-state leukapheresis for T-cell collection. A lentiviral vector is used to infect the T cells and transfer the new genetic material encoding the CAR. Modified cells undergo short-term culture for expansion and activation and are harvested for infusion after 12 to 14 days. Patients typically receive lymphodepleting chemotherapy before T-cell infusion. IL, interleukin; TCR, T-cell receptor. Adapted from Mato A, Porter DL, *Blood*. 2016;126(4):478-485, with permission from the publisher.

or hinge region, and the TCR CD3ζ chain without costimulatory domains. Unlike physiologic activation of T cells, this construct leads to activation of the engineered T cell upon contact with the target antigen in an HLA-independent manner. While effective in vitro, first-generation CARs have partial expansion and limited in vivo persistence, yielding limited clinical efficacy. Enhanced in vivo expansion and persistence of CAR T cells is achieved with second-generation CAR constructs that include a costimulatory domain (eg, CD28, 4-1BB, OX40). Even greater activation, proliferation, and efficacy is achieved with third-generation CARs that include 2 costimulatory domains although there is limited data to date that additional signaling impacts clinical outcomes. CAR constructs may be integrated into autologous or allogeneic T cells through lentiviral or retroviral transduction or electroporation of CAR-coding messenger RNA constructs. After ex vivo expansion, T cells are infused into patients following lymphodepleting chemotherapy (typically fludarabine with or without cyclophosphamide), which facilitates in vivo expansion by removal of regulatory T cells and generation of a supportive cytokine milieu (Figure 14-1).

Allogeneic CAR T-cell products

The initial CAR products all used autologous apheresis material that was genetically reengineered and infused back into the patient. Immunologically this approach mitigates the concerns for allogeneic reactions, both rejection of the CAR which can limit persistence or a GVHD-mediated response. However, because of prior lines of therapy which can damage T-cell populations and rapidly progressing disease, autologous CAR T is not feasible for all patients. Additionally, the process is time consuming, requires shipping to and from a third-party site, and is costly. The ability to use donor-derived allogeneic products that can be administered "off the shelf" has significant potential advantages to overcome current limitations. Donor-derived T cells manufactured from peripheral blood mononuclear cells or UCB have been used for allogeneic CAR T-cell therapy. To mitigate the

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavrillaki on 10 December 2022

risk of GVHD, several approaches including gene editing of the alpha-beta T-cell receptor and selection of γδ T cells for CAR manufacturing, among others, are under active investigation.

UCART19 is an anti-CD19, gene-edited, donor-derived CAR T-cell product that includes messenger RNA encoding the target *TRAC* and *CD52* genes to disrupt cell surface expression of TCR alpha-beta and CD52 to minimize GVHD. This construct has a CD20 target for rituximab to allow elimination of the UCART19 product in the setting of excessive toxicity. In a phase 1 clinical trial of UCART19 in pediatric and adult B-cell Acute Lymphoblastic Leukemia (ALL), 21 patients were treated, and 14 patients achieved a Complete Remission (CR) or CR with incomplete hematological recovery at 28 days postinfusion. Three patients had grade 3-4 cytokine release syndrome (CRS) and grade 1-2 neurotoxicity in 8 patients. There were 2 treatment-related deaths related to CRS and persistent cytopenias. Skin GVHD occurred in 2 patients. The PFS at 6 months was 27%. This trial demonstrates the real-world feasibility of allogeneic products, but additional trials with larger cohorts of patients and longer follow-up are indicated to determine its efficacy and safety.

Cancer therapy with T-cell receptor–engineered cells

Compared to CAR-modified T cells, adoptive cell therapy with autologous TCR-engineered T cells has garnered less attention as an approach to redirect T cells toward defined cancer antigens. TCR-engineered cells are most effective for the targeting of peptides from tumor- associated cell membrane or intracellular/nuclear proteins as they are presented on the cell surface by HLA molecules. This approach depends on the generation of TCR α and β chains specifically recognizing an intended tumor target and expressing engineered TCR molecules in autologous T cells. Efficient TCR gene transfer can be achieved with retroviral and lentiviral vectors or the nonviral sleeping beauty system, with each modality carrying a risk of insertional mutagenesis. In contrast to later-generation CAR constructs, current TCR engineering does not involve the introduction of extracellular stimulatory domains, so that gene-modified cells depend on the retention of natural TCR-signaling components for functionality. The ability of TCR-engineered cells to recognize the intended tumor cell depends on the cell surface abundance of the therapeutic TCR α/β heterodimer, as well as the receptor's affinity for the target antigen, aspects that need optimization (eg, to reduce mispairing with endogenous TCR chains, which could theoretically result in unexpected, self-reactive TCR specificities with potential to cause off-target autoimmunity).

Most experience with TCR-based adoptive cell therapy has been gained in patients with advanced solid tumors. Several small studies have tested TCRs directed at MART-1 and pg100 (metastatic melanoma), MAGE-A family members (primarily metastatic melanoma and esophageal cancer), CEA (colorectal cancer), and NY-ESO-1a (primarily metastatic melanoma and synovial sarcoma). In these studies, patients generally received ex vivo expanded, gene-modified autologous peripheral blood lymphocytes after administration of lymphodepleting chemotherapy (most commonly cyclophosphamide and fludarabine) and in conjunction with interleukin (IL)-2. Together, available data from these trials suggest the potential of TCR-engineered cells to exert clinically significant antitumor efficacy. However, in many cases, tumor responses were of short duration, and further methodological refinements are necessary to increase the in vivo persistence and functionality of these cells to maintain their anticancer effects. The clinical experience is limited in hematologic malignancies, but data from small studies reporting possible antitumor efficacy with the use of autologous T cells expressing TCRs against NY-ESOc259 (multiple myeloma) or WT1 (AML) suggest the benefit may extend to some patients with blood cancers as well. Several trials with TCR-engineered cells are currently ongoing and the clinical experience with these cells for the treatment of hematologic malignancies and solid tumors is likely to increase substantially over the next several years. These trials will also clarify the spectrum of associated toxicities. While infusion of ex vivo expanded TCR-modified cells was well-tolerated without significant safety concerns or apparent CRS in some trials, others have highlighted the potential toxicities of these cells. The use of higher-affinity TCRs, can cause adverse on-target, off-tumor as well as off-target toxicity and substantial morbidity and mortality (eg, inflammatory colitis [CEA], skin rash [MART-1, pg100], and cardiac/neurologic toxicity [MAGE-A]).

Natural killer cells

NK cells are part of the innate immune system and can exert antitumor and antimicrobial activity in an antigen-independent fashion. This activity is modulated by an intricate balance between various activating and inhibitory receptors, including the killer cell immunoglobulin-like receptors. Unlike T cells, NK cells do not require prior antigen sensitization to elicit cytotoxic effects and do not cause GVHD in the allogeneic setting, properties that render them very attractive for adoptive cell therapy.

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022

Recent efforts have focused on allogeneic NK cells. In this setting, enrichment of NK cells collected from the peripheral blood or from cord blood products is usually achieved by depletion of T and B cells, with or without additional positive selection of CD56-positive cells to enrich for NK cells. To increase the number of NK cells and improve their antitumor activity, a variety of protocols have been developed for the ex vivo expansion/activation of cells from healthy donors. Lymphodepleting conditioning chemotherapy with cyclophosphamide and fludarabine can facilitate NK cell persistence and expansion in vivo, possibly in part because it leads to high production of IL-15. Currently, efforts are ongoing to overcome limitations of NK cell therapy to modulate their persistence, cytotoxicity, and homing.

Recently one study reported outcomes of a phase 1 trial using anti-CD19 modified CAR-NK cells. For this product, cord blood units were the source of NK cells that were then transduced with anti-CD19 retroviral CD28/CD3ζ vector that also included genes for IL-15 and inducible caspase 9. Cells were expanded and infused fresh on day 15 in patients with relapsed, refractory B-cell non-Hodgkin lymphomas (NHLs). The administration of these cells was not associated with traditional adverse events such as CRS, neurotoxicity, or GVHD. Eight of 11 patients reported had a clinical response at first assessment. While CAR-NK cells persisted at low levels for at least 12 months, longer follow-up is needed to better determine the duration of response.

Tumor-infiltrating lymphocytes

A unique form of adaptive cell therapy involves the use of autologous T cells collected from resected tumor material. These tumor-infiltrating lymphocytes are subsequently expanded ex vivo and delivered back into the patient in the presence of cytokines and have led to impressive outcomes in refractory solid malignancies. TILs are delivered in combination with IL-2 to improve antitumor activity with improved outcomes seen with high-dose IL-2 in comparison to low-dose IL-2. Similar to other adoptive cell therapies, a preparative regimen of chemotherapy to lymphodeplete the patient is applied to improve persistence of the infused T cells in vivo. TIL therapy has been shown to lead to durable responses in patients with refractory solid malignancies including melanoma, cholangiocarcinoma, non–small cell lung cancer, etc. Several pharmaceutical companies are advancing TIL therapies with anticipation of approved products in the imminent future. Challenges to TIL therapy is the need to manufacture a personalized product for each individual patient.

The hematopoietic cell transplantation process

The HCT process begins with the administration of a conditioning regimen of chemotherapy and sometimes radiation to eradicate a malignant disorder or a poorly functioning bone marrow. Allogeneic HCT also requires the administration of immunosuppressive, lymphotoxic chemotherapy to promote donor engraftment, sometimes with T-cell–depleting antibody therapy to reduce the risk of GVHD. The conditioning regimen is followed by reinfusion of HPCs from the patient (autologous) or allogeneic donor. Intense medical support is required as patients recover from the effects of the conditioning regimen and during the period of immune suppression that occurs while the transplanted HPCs mature. Because of this complexity, national standards exist for care of transplant patients, and centers are accredited by the Foundation for the Accreditation of Cellular Therapy as a designation that they meet this standard.

Indications for hematopoietic cell transplantation

HCT is performed for a variety of malignant and nonmalignant hematologic disorders. The most common indications for HCT are summarized in Table 14-2 and data for each indication are summarized later in this chapter.

Transplant eligibility

Having a condition amenable to treatment with HCT is not enough for a patient to be eligible for transplant. Transplant eligibility is determined by a comprehensive pretransplant evaluation, which includes assessment of comorbidities, organ function, and psychosocial factors to estimate the ability of a patient to tolerate transplantation and the risk-benefit of HCT compared with less toxic treatment approaches. Table 14-3 summarizes the most used criteria to determine HCT eligibility which includes the HCT-comorbidity index (HCT-CI), a standard measurement that predicts risk of NRM in HCT recipients.

Age

Individuals with comorbidities and those 70 years of age and older are now eligible to undergo allogeneic HCT, following the introduction of reduced-intensity or nonmyeloablative conditioning regimens, which have resulted in a decrease in regimen-related morbidity and mortality. Between 1991 and 1997, 7% of allogeneic HCTs were performed in patients over 50 years old; between 2000 and 2015, this percentage increased to 38%. In 2015, 25% of all allogeneic HCT recipients were patients over 60 years old, compared to 5% in 2000. Recent analyses

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavrillaki on 10 December 2022

Table 14-2 Most common indications for HCT

Autologous HCT		Allogeneic HCT	
Diagnosis	No. performed in the United States, 2015	Diagnosis	No. performed in the United States, 2015
Multiple myeloma	7400	Acute myeloid leukemia	3200
Non-Hodgkin lymphomas	3000	Acute lymphoblastic leukemia	1300
Hodgkin lymphoma	900	Myelodysplastic syndromes	1100
		Non-Hodgkin lymphoma	770
		Myeloproliferative neoplasms	540
		Severe aplastic anemia	340

HCT, hematopoietic cell transplantation.

have suggested similar outcomes in patients over 65 to 70 for both autologous and allogeneic HCT when compared to younger populations as long as recipients were appropriately selected. This suggests that age alone is a less reliable predictor of outcome and must be considered in the context of comorbidities and fitness.

Table 14-3 Commonly used eligibility criteria for HCT

Eligibility criteria	Test	Transplant eligible	Comments
Patient performance status	Medical history	ECOG performance status 0-2, Karnofsky performance status >70%	Transplant mortality increases with decreasing pre-HCT performance status. Patients with poor performance status generally are not considered candidates for HCT.
Disease and disease status	Multiple	Depending on disease, disease risk, and disease status. High-risk disease and high-risk disease status predict <10% 2-year survival	Patients with advanced refractory disease are generally not transplant eligible. Armand et al. proposed a disease and disease status risk classification for HCT.
Infectious disease markers	Serologies for hepatitis A, B, and C. PCR for viral copies HIV, HTLV-1, CMV, EBV, toxoplasmosis	Generally, patients should not have documentation of active viral replication	Guidelines changing with the advent of effective antiviral therapy for HIV, HBV, and HCV. Prior hepatitis exposure does not affect transplant outcomes.
Cardiac function	Echocardiogram Nuclear medicine testing	Ejection fraction >40% No uncontrolled cardiac disease	Patients with cardiac disease may require more extensive pretransplant evaluation, including referral to cardiology for stress testing or Holter monitoring.
Pulmonary function	Pulmonary function testing	DLCO >40%	In some series, the most important predictor of outcome is DLCO <40%.
Renal function	Creatinine and creatinine clearance	Creatinine clearance >40 cc/min	Patients with poor renal function can be considered for HCT. Autologous HCT is performed for patients with multiple myeloma on dialysis.
Hepatic function	Liver function tests (transaminases and bilirubin)	Bilirubin <2-3 × ULN unless Gilbert disease	Elevated liver function tests predict liver toxicity.
Comorbidity scoring	Hematopoietic cell transplantation specific comorbidity indices	No cutoff determined. Poor risk categories predict increased treatment-related mortality	Comorbidity scoring is useful to guide regimen intensity and for estimation of transplant-related mortality. HCT-CI most commonly used scoring system.
Psychosocial	Various	Varies by institution	Essential to determine risk of noncompliance, substance abuse, caregiver availability, and social support needed throughout the transplant process.

CMV, cytomegalovirus; DLCO, diffusing capacity for carbon monoxide; EBV, Epstein-Barr virus; ECOG, Eastern Cooperative Oncology Group; HCT, hematopoietic cell transplantation; HCT-CI, hematopoietic cell transplantation-comorbidity index; HTLV-1, human T-lymphotropic virus 1; PCR, polymerase chain reaction; ULN, upper limit of normal.

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022

Table 14-4 Commonly used conditioning regimens

Allogeneic hematopoietic cell transplantation	
Myeloablative conditioning	
Cy TBI	Cyclophosphamide 120 mg/kg + TBI 8-12 Gy★
Bu Cy	Cyclophosphamide 120 mg/kg + busulfan 9.6-12.8 mg/kg IV or PO equivalent
Flu Bu	Fludarabine 120-150 mg/m^2 + busulfan 9.6-12.8 mg/kg IV or PO equivalent
Reduced-intensity conditioning	
Flu Mel	Fludarabine + melphalan 140 mg/m^2
Flu Bu	Fludarabine + busulfan 6.4 mg/kg IV or PO equivalent
Nonmyeloablative conditioning	
Flu TBI	Fludarabine + TBI 2 Gy
Flu Cy	Fludarabine + cyclophosphamide 60 mg/kg
Cy ATG	Cyclophosphamide 4 g/m^2 + ATG†
Autologous hematopoietic cell transplantation (all myeloablative)	
Lymphoma	
BEAM	BCNU + etoposide + cytarabine + melphalan
BEAC	BCNU + etoposide + cytarabine + cyclophosphamide
CBV	Cyclophosphamide + BCNU + etoposide
Myeloma	
High-dose melphalan	Melphalan 200 mg/m^2

ATG, antithymocyte globulin; BCNU, Carmustine intravenous; TBI, Total Body Irradiation.

★Various fractionation schedules in use.

†Mainly for conditioning in severe aplastic anemia.

Conditioning regimens

The combination of chemotherapeutic agents given prior to HCT is known as the *conditioning* or *preparative regimen*. The purpose of conditioning in both the autograft and allograft setting is to eradicate the malignancy with high-dose chemotherapy or radiation therapy. In the setting of allogeneic HCT, the conditioning regimen also suppresses the recipient's immune system to prevent rejection of donor hematopoietic cells. The more immunosuppressive the conditioning regimen is to the host, the better the chance for engraftment. Conditioning regimen intensity is classified according to myelosuppressive effects into the categories of fully myeloablative (MAC), RIC, and non-myeloablative (NMA). Table 14-4 lists commonly used conditioning regimens.

Myeloablative regimens

The first conditioning regimen that achieved widespread application combined cyclophosphamide and total body irradiation (CyTBI). High doses of cyclophosphamide, typically 120 to 200 mg/kg, are combined with radiation in a dose of 8 to 12 Gy. This regimen is myeloablative and profoundly immunosuppressive. High-dose busulfan and cyclophosphamide (BuCy) conditioning was developed as an alternative to CyTBI. Treatment-related morbidity and mortality rates are similar after both regimens, although the patterns of toxicity are slightly different. TBI is associated with more pulmonary toxicity, cataract formation, and thyroid dysfunction. BuCy is associated with a higher incidence of sinusoidal obstruction syndrome of the liver (SOS; formerly veno-occlusive disease [VOD]), though this is much less likely with IV busulfan and pharmacokinetic-guided dosing, and irreversible alopecia. Fludarabine/busulfan combinations have become increasingly used because cyclophosphamide and its metabolites increase the risk of SOS/VOD.

Nonmyeloablative and reduced-intensity conditioning

MAC regimens were long considered necessary for engraftment of allografts, but their considerable extramedullary toxicity limited their use to patients more than 50 years old who had a good performance status and no comorbidities. The demonstration that engraftment can be achieved without myeloablation led to the development of NMA and RIC regimens. These regimens use lower doses of busulfan, melphalan, cyclophosphamide, or TBI (typically 2 Gy), often in combination with fludarabine for immune suppression. NMA and RIC regimens are more frequently used in older patients, in patients with comorbidities, and in nonmalignant bone marrow disorders. For malignant conditions, these regimens rely heavily on immunologic (GVT or graft-versus-leukemia [GVL]) effects to achieve long-term remissions and contain lower doses of drugs with cytoreductive activity and are associated with a higher risk of relapse. Although treatment-related deaths are less frequent with NMA/RIC regimens compared to myeloablative regimens, GVHD and infections remain the major causes of NRM.

Operationally, RIC regimens have been defined by the following doses of commonly administered agents: melphalan (<150 mg/m^2); busulfan (<9 mg/kg of the oral equivalent); thiotepa (<10 mg/kg); and TBI (<500 cGy single fraction or 800 cGy fractionated). These definitions are somewhat arbitrary but are important for retrospective studies.

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022

The optimal conditioning intensity for patients for malignant hematologic disorders was informed by the BMT CTN trial in patients with AML or Myelodysplastic Syndrome (MDS) randomized to RIC or fully MAC allogeneic HCT. The study was stopped early because of a high relapse rate in the RIC arm. Overall survival at 18 months was 68% in the RIC arm versus 78% in the myeloablative arm ($P = 0.07$). Transplant Related Mortality (TRM) was 4.4% for RIC versus 16% with MAC ($P = 0.002$), whereas relapse-free survival was 47% with RIC versus 68% with MAC ($P < 0.01$). Based on these results, MAC may be preferred for fit adult patients with AML or MDS.

Regimens for autologous hematopoietic cell transplantation

Given the lack of GVT effect with autologous transplantation, all regimens are myeloablative to attempt to cure or control disease with high-dose chemotherapy. Preparative regimens include: (1) carmustine, etoposide, cytarabine, and melphalan (BEAM), or cyclophosphamide, carmustine, and etoposide for relapsed/refractory (R/R) non-Hodgkin lymphoma or Hodgkin lymphoma (HL); (2) high-dose melphalan regimens used for multiple myeloma; and (3) the carboplatin and etoposide regimen for relapsed germ cell tumors. Conditioning for a nonmalignant condition such as severe scleroderma includes TBI (800 cGy), cyclophosphamide (120mg/kg), and equine antithymocyte globulin (ATG) (90mg/kg) and the data supporting cell transplantation for this and other autoimmune conditions continue to grow.

Conditioning for nonmalignant hematologic disorders

Patients with aplastic anemia, autoimmune disorders, metabolic disorders, or hemoglobinopathies represent a special category. There is no underlying malignancy that requires eradication. There is also a higher risk of graft rejection because of the nature of the underlying disease, the lack of previous immunosuppressive chemotherapy and, in many cases, exposure to prior transfusions with HLA sensitization. Thus, the conditioning regimens for such patients traditionally have emphasized more immunosuppression and less myelosuppression. A combination of high-dose cyclophosphamide with ATG has emerged as the standard conditioning regimen for aplastic anemia. Conditioning therapy is more challenging for patients with Fanconi anemia because of excessive toxicity from cyclophosphamide in these patients.

Phases of hematopoietic cell transplantation

Successful HCT requires the patient to tolerate the conditioning regimen; HPCs to engraft, proliferate, and mature normally; adequate prevention and treatment of infectious complications related to myelosuppression and immunosuppression after HCT; and, in the case of allogeneic HCT, prevention and treatment of GVHD. Outcomes are improved when HCTs are performed in specialized transplant units that perform a minimum of at least 10 transplants a year. The HCT procedure can conceptually divided into 5 phases, though there is significant variability in the timing and progression through each phase based on the type of transplant (auto versus allo), recipient factors, preparative conditioning, T-cell depletion and GVHD prophylaxis used, and other variables. An overview is provided in the following sections and summarized in Table 14-5.

Phase I: conditioning (start of preparative regimen to day 0)

During this phase, the conditioning regimen is given to the patient to eliminate any residual malignant cells, provide physical space for the donor stem cells and, in the case of allogeneic HCT, suppress the recipient immune system to facilitate donor cell engraftment. This phase finishes with the infusion of the hematopoietic cells provided either by the patient in the case of an autologous HCT or by a donor in the case of an allogeneic HCT.

Phase II: cytopenic phase (day 0 to engraftment)

The most obvious effects of the conditioning regimen are noted during this phase. Severe myelosuppression and disruption of the gastrointestinal (GI) mucosa manifesting as stomatitis and diarrhea can last 10 to 28 days. During this period, serious infections and organ toxicities such as SOS/VOD and idiopathic pneumonia syndrome (IPS) can occur.

Phase III: early recovery

Within the first few days to weeks of neutrophil recovery, patients can develop a syndrome characterized by fever, rash, and pulmonary infiltrates known as the *engraftment syndrome*, which should be treated promptly with corticosteroids. This period also marks the time when GVHD may begin to manifest in the allograft setting.

Phase IV: immune reconstitution

This phase is characterized by persistent immune deficiency despite normal peripheral blood cell counts. Allogeneic recipients remain at risk of serious life-threatening opportunistic infections that require antibacterial, antiviral, and antifungal prophylaxis for at least many months posttransplant as well as close monitoring for infection by the transplant team. Autologous recipients

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022

Table 14-5 HCT complications according to transplant phase

	Phase I: conditioning	Phase II: cytopenic phase	Phase III: early recovery	Phase IV: early convalescence	Phase V: late convalescence
Timing	D−10 to D0	D0 to engraftment	Engraftment + 7 d	D+30 to 6-12 months	>12 months
Infections	Catheter-related	GPC, GNR from GI mucosal toxicity HSV Fungal infections Catheter-related	Resistant GNR or GPC Fungal infections CMV reactivation EBV reactivation Other viruses	Viral reactivations *Pneumocystis* Encapsulated GPC EBV^+ PTLD	Viral reactivation (if active GVHD) Encapsulated GPC
Gastrointestinal	Nausea and vomiting Diarrhea	Mucositis Diarrhea Nausea Anorexia	Protracted nausea and/or anorexia can be sign of upper GI GVHD	Gut GVHD: diarrhea, abdominal pain, nausea, anorexia	
Hepatic	Transaminitis	Transaminitis Sinusoidal obstruction syndrome	Transaminitis Sinusoidal obstruction syndrome Liver GVHD	Hepatitis virus reactivation Liver GVHD	Cirrhosis
Cardiac	Arrhythmias (rare) Fluid overload	Hypertension from CNI	Hypertension from CNI	Hypertension from CNI	Congestive heart failure Premature coronary vascular disease
Pulmonary	Pneumonitis (rare)	Infectious pneumonia Fluid overload Idiopathic pneumonia syndrome	Infectious pneumonia Idiopathic pneumonia syndrome Diffuse alveolar hemorrhage	Cryptogenic organizing Infectious pneumonia	Bronchiolitis obliterans syndrome Hyperactive airway disease Infectious pneumonia
Neurologic	Seizures from busulfan (rare with prophylaxis)	PRES (from CNI)	PRES (from CNI)	PRES (from CNI)	Cognitive dysfunction—short-term memory loss Impaired concentration
Endocrine	Hyperglycemia	Hyperglycemia from CNI	Hyperglycemia from CNI	Hyperglycemia Hypothyroidism	Metabolic syndrome
Renal	Increased creatinine Electrolyte abnormalities	Increased creatinine because of drugs (antibiotics, antifungals, CNI) Electrolyte disturbances	Increased creatinine Electrolyte disturbances	Chronic renal failure	Chronic renal failure
Acute graft-versus-host disease			Initial presentation can be rash and fevers	Late acute GVHD presents as acute onset diarrhea, rash, transaminitis, or hyperbilirubinemia	
Chronic graft-versus-host disease				Usually presents in the context of immune suppression withdrawal	Usually presents in the context of immune suppression withdrawal
Other				PTLD	Cataracts Secondary malignancies

CMV, cytomegalovirus; CNI, calcineurin inhibitor; EBV, Epstein-Barr virus; GI, gastrointestinal; GNR, gram-negative rods; GPC, gram-positive cocci; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; HSV, herpes simplex virus; PRES, posterior reversible encephalopathy syndrome; PTLD Post-Transplant Lymphoproliferative Disorder.

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022

have more rapid immune reconstitution when compared to allogeneic recipients. Patients undergoing allogeneic HCT continue to be at risk for acute as well as chronic GVHD, and treatment for GVHD further delays immune reconstitution. Those undergoing reduced-intensity transplants may also develop late-onset acute GVHD beyond day 100. Late organ side effects may arise, especially lung toxicities such as cryptogenic organizing pneumonia and bronchiolitis obliterans syndrome (BOS). Relapse risk is highest in the first 2 years after transplant, and risk of infection can persist long after transplant as well.

Phase V: late recovery

This final phase is characterized by the almost full recovery of the immune system and the potential of late complications, such as organ dysfunction, cataracts, secondary malignancies, or recurrence of the original malignancy. Patients undergoing allogeneic HCT remain at risk of developing chronic GVHD and infections.

Hematopoietic cell transplantation complications

Myelosuppression

Myelosuppression is a universal complication of MAC regimens. The duration of the myelosuppression depends on various factors, including the hematopoietic stem cell dose, GVHD prophylaxis, extent of prior therapy, and stem cell source (peripheral blood versus bone marrow versus UCB). Engraftment is defined as an absolute neutrophil count of >500/μL and platelets >20,000/μL, (without transfusion the past 7 days) respectively, on the first of 3 consecutive days above that threshold. Filgrastim has been shown to reduce the time to neutrophil engraftment in both the autologous and allogeneic setting but without definitive improvement in HCT outcomes such as Overall Survival (OS).

Graft failure

The mechanisms of graft failure include immunologic rejection, abnormalities in the marrow microenvironment or stroma, inadequate cell dose or composition of the graft, viral infections (in particular CMV), or drug-induced myelosuppression. The risk for graft failure is increased with increasing HLA disparity between the graft and host, with T-cell depletion of the graft, the use of bone marrow or cord blood as a stem cell source, and in transplantation for severe aplastic anemia or hemoglobinopathies. Specifically, the BMT CTN 0201 study reported a graft failure rate of 9% for bone marrow grafts compared to 3% for peripheral blood HPCs. The risk for graft rejection can be decreased by infusing larger numbers of HPCs and by increasing the intensity of the conditioning regimen. Successful treatment of graft failure involves reinfusing more stem cells either from the original stem cell donor or another source if the original donor is unavailable. Graft failure after autologous HCT is rare but can happen because of infections, toxic drug exposure, or inadequate cell dose.

Infection

Infections are a major cause of life-threatening complications in HCT; major advances in this area have decreased TRM. The Infectious Disease Society of America/American Society of Transplantation and Cell Therapy recommendations from 2009 provide a framework for treatment and prevention.

Bacterial infections commonly occur during the neutropenic period after transplantation, and guidelines for prevention and management are similar to those in other neutropenic patients. The use of prophylactic fluoroquinolone antibiotics is standard for patients >12 years old during the neutropenic period. Patients with chronic GVHD are also immunosuppressed and at particular risk for fulminant infections with encapsulated gram-positive organisms, particularly *Pneumococcus*. They should receive prophylaxis with penicillin v Potassium (VK). While elimination of pathogenic bacteria remains a requirement for successful transplant outcomes, there is an increasing appreciation for the role of the microbiome after the demonstration that a more diverse microbiota at the time of neutrophil engraftment led to lower mortality. This has now led to the study of fecal transplantation as an intervention in HPC transplant recipients.

HCT patients are at high risk for *Pneumocystis jirovecii* pneumonia and prophylaxis is recommended with trimethoprim-sulfamethoxazole (TMP-SMX). For those allergic to TMP-SMX, alternatives such as pentamidine, atovaquone, or dapsone are commonly used but are less effective. TMP-SMX prophylaxis also helps prevent toxoplasmosis, which has been reported in recipients of allogeneic transplantation.

Fungal infections remain a risk in allogeneic transplantation patients and risk increases in the setting of prolonged neutropenia, immunosuppression, corticosteroids, and GVHD; though these infections are becoming less common in the setting of effective prophylaxis and the use of PBSC grafts allowing earlier neutrophil recovery. Yeast (*Candida* species) infections are rare with prophylaxis and are typically caused by fluconazole-resistant organisms. Airborne molds, particularly *Aspergillus* species, remain a risk for patients undergoing allogeneic transplantation, despite the use of high efficiency particulate air

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022

filtration. Mold-active azoles (eg, voriconazole, posaconazole, isovuconazole) and echinocandins (eg, caspofungin, micafungin, anidulafungin) have improved the outcome of these infections. Broad-spectrum azoles such as posaconazole and isovuconazole are often used for prophylaxis of fungal infections in patients undergoing allogeneic HCT and those receiving higher doses of systemic corticosteroids for GVHD therapy. Interactions of azoles with the metabolism of calcineurin inhibitors warrant the need for careful monitoring and dose adjustment of tacrolimus and cyclosporine. In the setting of better control and prevention of aspergillosis, cases of mucormycosis are increasingly reported and necessitate treatment with amphotericin derivatives and surgical resection, though azoles such as posaconazole and isovuconazole have limited activity versus mucor.

Viral infections are common after HCT. CMV infection used to be a major cause of pneumonia and death in HCT recipients but is now much less common because of aggressive prevention and preemptive treatment of viral reactivation. CMV infection post-HCT usually occurs because of CMV reactivation in recipients previously exposed to CMV as indicated by positive antibody titers (CMV-seropositive patients) before transplant. The incidence of reactivation without prophylaxis ranges from 40% to 60% in the allogeneic setting and <5% in the autologous setting. Detection of CMV in the blood (CMV viremia), either by PCR or rapid antigen screening, indicates a high risk for development of invasive CMV disease, usually CMV pneumonia, but hepatitis, retinitis, or gastroenteritis are also possible. Patients who have not been exposed before transplantation (CMV−) are still at risk for CMV infection either by transmission from a CMV+ HPC donor or via transfusion of blood products from a CMV+ blood donor. To avoid risk of CMV infection in CMV seronegative donor/recipient pairs, CMV-safe blood products such as leukocyte-reduced products are required.

Frequent screening for CMV viremia is mandatory in the first 3 months after allogeneic HCT. Letermovir, a novel antiviral that inhibits the CMV-terminase complex, is the most common medication used for primary prophylaxis. A phase 3 randomized study of letermovir versus placebo as primary prophylaxis after allogeneic HCT showed a significant reduction in clinically significant CMV infection (CMV reactivation requiring preemptive therapy or invasive CMV disease) from 61% with placebo to 38% with letermovir ($P < 0.001$) without a difference in invasive CMV disease or death from any cause. Preemptive therapy options include ganciclovir, valganciclovir, and foscarnet. Each of these approaches has potential adverse effects. Myelosuppression, especially neutropenia, is a common toxicity associated with ganciclovir and valganciclovir, while electrolyte abnormalities and renal injury are more common with foscarnet. Acyclovir and valacyclovir have no role in preemptive CMV treatment, though maribavir may have some role.

Other important herpes viruses include herpes simplex virus (HSV), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), and human herpesvirus 6 (HHV-6). HSV, previously a major cause of early mucositis and pneumonia, and VZV are now effectively prevented with acyclovir or valacyclovir prophylaxis. A double-blinded study of HSV/VZV prophylaxis compared to placebo showed a hazard ratio of 0.16 ($P = 0.006$) for VZV infections within 1 year of transplant. EBV can cause posttransplantation lymphoproliferative disease, particularly in patients who are extremely immunosuppressed because of mismatched or T-cell–depleted transplantation. Withdrawal of immune suppression is performed when possible to stimulate an immune response against EBV-infected cells; treatment with rituximab is typically first-line therapy. HHV-6 frequently reactivates after allogeneic HCT and may cause posttransplantation encephalitis, hepatitis, or aplasia, but does not require aggressive preemptive therapy in most cases. BK viruria is associated with hemorrhagic cystitis and is treated with hydration and lowering immune suppression as able.

Adenovirus can cause fatal hepatitis, gastroenteritis, and pneumonitis in transplantation patients. The value of screening and role of preemptive therapy is uncertain, but infection is more common in recipients with delayed immune reconstitution or T-cell depletion. Treatment is generally with cidofovir, dosed once weekly, which has significant risks of nephrotoxicity, and myelosuppression. Brincidofovir is also active against adenovirus, though GI toxicity is a notable adverse effect.

Respiratory viruses, such as respiratory syncytial virus (RSV) and influenza virus, can lead to fatal pneumonias after HCT and warrant strict infectious prevention measures at transplant centers. Lower respiratory tract infection with RSV is treated with ribavirin, usually inhaled, though oral treatment is also available. Many other respiratory viruses can cause significant complications in the posttransplant setting when they cause lower respiratory tract infection such as influenza, parainfluenza, and even rhinovirus. Beginning in 2020, infection with SARS-CoV-2 was associated with very high rates of complications, with 14% of patients requiring mechanical ventilation and a 30-day survival in all patients of 68%. Research performed during the COVID-19 pandemic also demonstrated the benefit of face masks for the prevention of respiratory viral infection.

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022

Finally, transplant recipients who previously lived in areas with high rates of strongyloidiasis, such as Central America, should be screened and/or treated with ivermectin prior to transplant since this infection can flare and cause significant symptoms in the posttransplant setting. The presentation post-HCT may also resemble GVHD and should be included on the differential in at-risk recipients.

T-cell therapy for the treatment of viral infections

The frequency of opportunistic viral infections in allogeneic HCT recipients, combined with inadequacies and toxicities of current pharmacological therapies, has raised interest in strategies to prevent or treat these infections and their sequelae and to establish long-term immunological memory.

One approach to accomplish this goal includes adoptive cell therapy with prophylactic or therapeutic infusion of donor-derived or third-party ("off the shelf") virus-specific T cells. Several techniques have been established for T-cell production that vary in the way antigens are presented and T cells are selected and expanded. The methodologies have evolved rapidly, and solutions have been developed that adhere to good manufacturing practices and overcome limitations identified in early clinical studies. As one example, rather than coculturing T cells and antigen-presenting cells (APCs) loaded with virus-derived peptides, proteins, or viral lysates, overlapping peptide libraries (called *pepmixes*) derived from full-length immunodominant viral proteins are pulsed into donor-derived APCs as immunogens and cultured with T cells. Alternatively, APCs can be genetically engineered to present immunogenic viral peptides to T cells. Both approaches allow the development of multivirus-specific T cells and can be used for the generation of cell product from naïve cord blood lymphocytes. Also in line with good manufacturing practices are direct-selection techniques via IFN-γ capture or through multimer- based selection that allow rapid generation of virus-specific T cells and scalability of products. Adoptive cell therapy with donor-derived, virus-specific T cells has been developed in many centers and used to prevent and/or treat viral infections. Results from early phase trials demonstrate that such cells are safe and can be highly effective in controlling CMV and EBV infections in HCT recipients, conferring protection in up to 70% to 90% of patients. EBV-specific T cells have also shown remarkable efficacy in the prevention of EBV+ lymphomas posttransplant, as well as the treatment of established EBV lymphomas with achievement of sustained complete remissions in the majority of patients. In some patients, failure to respond or loss of response has been associated with the presence of viral strains that possess deletions in immunodominant epitopes or origination of virus-associated tumor cells in recipient rather than donor cells. In recent years, the spectrum of infections targeted with pathogen-specific (or multipathogen-specific) T cells has expanded to include additional viruses seen in immunocompromised patients (eg, adenovirus, VZV, HHV-6, polyomaviruses [BK virus, JC virus, and Merkel cell carcinoma virus)], influenza) and fungi (eg, *Aspergillus*).

Third-party products from banks of cryopreserved virus-specific T cells offer readily available therapy that can overcome the need for patient-specific T cell manufacturing. Closely matched third-party products yielded responses in up to 70% of patients with resistant CMV, EBV, or adenovirus infection. However, while third-party products do not require full HLA matching to the recipient for antiviral activity, identification of closely matched products can be difficult, and suboptimal HLA matching has been associated with lack of T-cell expansion in recipients. These products also have the theoretical concern of alloreactivity, but an increased risk of GVHD has so far not been observed clinically.

Specific organ toxicities

Gastrointestinal toxicity

Second to hematopoietic cells, the GI tract is the organ most affected by the conditioning regimen. As intestinal mucosa cells divide rapidly to maintain intestinal mucosal integrity, the GI tract is particularly susceptible to damage by conditioning regimens. The most common manifestations of GI toxicity are nausea, vomiting, mucositis (stomatitis), throat pain, esophagitis, abdominal pain, and diarrhea.

Destruction of the GI mucosa is a significant dose-limiting complication of high-dose therapy regimens as severe toxicity can lead to airway obstruction, mucosal bleeding, sepsis from intestinal flora, and intestinal perforation. In the setting of TBI-based conditioning, kepivance has shown some benefit in decreasing mucositis-related complications.

An effective prevention measure that limits the severity of mucositis in patients receiving high-dose melphalan is cryotherapy, the practice of using ice to cool the oral mucosa throughout the time surrounding dose administration. This decreased in the incidence of grade 3 mucositis from 74% to 14% ($P = 0.0005$) in a prospective randomized study.

Hepatic complications

SOS/VOD of the liver is a potentially fatal toxicity of HCT. Incidence varies depending on risk factors for patients including pre-HCT therapy, conditioning

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavrillaki on 10 December 2022

regimen, age, GVHD prophylaxis, and underlying liver disease. SOS/VOD is caused by preparative regimen toxicity and is thought to be caused by damage of endothelial cells, sinusoids, and hepatocytes in the area surrounding terminal hepatic venules leading to a local prothrombotic state.

Conditioning regimens associated with a higher risk of SOS/VOD include high-dose cyclophosphamide, prolonged and elevated busulfan levels (making individual pharmacokinetics and IV administration of busulfan beneficial for patient outcomes), or >12 Gy TBI. Pre-HCT therapy with gemtuzumab ozogamicin or inotuzumab ozogamicin also increases risk, especially in patients who receive the drug shortly before transplantation. Ursodiol and prophylactic heparin/LWMH are used for prevention of SOS/VOD though without definitive data demonstrating efficacy.

A diagnosis of SOS/VOD following the Baltimore criteria within the first 21 days after HCT requires a bilirubin of ≥2 mg/dL with 2 of the following: painful hepatomegaly, weight gain >5%, or ascites. Modified Seattle criteria are similar. Diagnosis can be aided by a transvenous procedure to measure intrahepatic pressures with simultaneous liver biopsy. Hepatic wedge pressure over 10 mm Hg is highly suggestive of SOS/VOD. Late-onset SOS/VOD beyond day 21 is much less common. Severe SOS/VOD is associated with multiorgan dysfunction and a mortality rate of ~80% if untreated.

Defibrotide is an approved medication for the treatment of SOS/VOD with associated multiorgan failure. While its mechanism of action is not fully understood, it is thought to contribute to endothelial cell stabilization by increasing tissue plasminogen activator and thrombomodulin while decreasing von Willebrand factor. Defibrotide has little systemic anticoagulant activity, which is an advantage in patients with multiorgan failure. Complete resolution of SOS/VOD by day 100 was seen in 25.5% of patients treated with defibrotide compared with 12.5% of historical controls ($P = 0.016$) while survival at day 100 was 38% with defibrotide treatment compared with 25% in the control arm.

Pulmonary toxicities

Pulmonary complications are common after HCT and contribute to post-HCT mortality. During the early transplantation period (days 0 to +30), regimen-related toxicity and infection account for most pulmonary events. Although most lung infiltrates are infectious, diffuse infiltrates related to regimen-related toxicity and other noninfectious etiologies should be considered such as IPS and diffuse alveolar hemorrhage (DAH).

Idiopathic pneumonia syndrome

IPS is characterized by diffuse alveolar injury often with fever, cough, dyspnea, hypoxemia, and restrictive airway physiology. Chest x-ray usually demonstrates multilobar pulmonary infiltrates. IPS requires exclusion of other causes of lung injury especially infection, pulmonary edema, and DAH. Bronchoalveolar lavage (BAL) must be negative for infectious etiologies, including bacteria, fungi, CMV, and other viral infections. The incidence of IPS is approximately 7%, with a median time to onset of 21 days and mortality ranging from 30% to 70%. The risk factors for IPS include the use of TBI or carmustine-based conditioning regimens and previous exposure to bleomycin. HHV-6 reactivation commonly accompanies IPS but a causative role for HHV-6 has not been established. Treatment of IPS is mostly supportive, though high-dose corticosteroids are often given with unclear benefit. Based on laboratory results suggesting that the inflammatory cytokine TNF-α plays a role in IPS, the TNF-α blocker etanercept has been studied as an adjunct to corticosteroids with improved survival compared with historical experience.

Diffuse alveolar hemorrhage

DAH occurs most commonly in the first weeks after HCT and presents as idiopathic pneumonia with or without hemoptysis. Unlike IPS, the classic finding on BAL is increasingly bloody returns during BAL washings. Analysis of BAL fluid usually demonstrates red blood cells, hemosiderin-laden macrophages if blood has been present for more than 2 to 3 days, and negative microbiologic studies. Treatment of DAH is largely supportive, but retrospective studies suggest that high-dose corticosteroids starting in the range of 1 g per day of methylprednisolone may be beneficial.

Transplantation-related obstructive airway disease

Approximately 6% to 10% of patients with chronic GVHD develop chronic airway obstruction. The most common histologic finding is constrictive BOS. BOS typically presents 3 to 12 months after an allogeneic HCT with gradual onset of dyspnea, dry cough associated with occasional wheezing, and inspiratory crackles. Pulmonary function tests demonstrate an obstructive airflow pattern that does not respond to bronchodilator therapy and a reduced diffusing capacity for carbon monoxide. Thin-section computed tomographic scans reveal bronchial dilatation, mosaic pattern attenuation, and evidence of air trapping on expiration. The diagnosis often is based on clinical, imaging, and spirometric findings without a tissue biopsy. Therapy for BOS includes treatment of GVHD as well as an inhaled

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022

steroid such as fluticasone along with azithromycin and montelukast. Importantly, azithromycin should not be used without confirmed GVHD of the lungs because of the association with a higher risk of cancer relapse post-HCT. Lung transplantation is an option for select patients.

Neurologic toxicities

Significant neurologic toxicity complicates approximately 10% to 20% of allogeneic HCT, usually within the first 100 days, but is rarer with autologous HCT. Many neurologic toxicities associated with allogeneic HCT are related to medications used either in conditioning or for GVHD prophylaxis but concurrent Central Nervous System (CNS) infections (such as HSV, VZV, HHV6, and CMV, among others) may also contribute. Busulfan conditioning increases the risk of seizures, though antiepileptic prophylaxis can prevent almost all such events. Posterior reversible encephalopathy syndrome (PRES) is associated with the use of calcineurin inhibitors and typically presents in the early posttransplant period with headache, confusion, vision changes, hypertension, and possible seizures. A brain MRI typically shows T2 enhancement in the white matter of occipital lobes, although similar lesions may be seen in the cerebellum and brainstem. Calcineurin inhibitors are the typical causative agent, although PRES has also been associated with exposure to etoposide and sorafenib. PRES typically resolves completely after withdrawal of the offending agent or treatment of the underlying cause.

Thrombotic microangiopathy

Transplantation-associated thrombotic microangiopathy (TA-TMA) presents as microangiopathic hemolytic anemia and occurs more commonly after allogeneic and unrelated donor HCT. In most patients, TA-TMA is related to calcineurin inhibitors (cyclosporine, tacrolimus) and usually responds to discontinuing the medication. Fungal infection, sepsis, or GVHD may also trigger the microangiopathic processes. Unlike patients with idiopathic Thrombotic Thrombocytopenic Purpura (TTP), patients with TA-TMA have preserved ADAMTS13 levels and do not respond to plasma exchange. Increased complement pathway activation has been associated with fatal TA-TMA and blocking the complement pathway with the C5-binding antibody eculizumab has some benefit as a treatment for TA-TMA, especially those with evidence of complement pathway activation.

Graft-versus-host disease

Acute GVHD and chronic GVHD were traditionally defined by the timing of onset. Acute GVHD was defined as any GVHD occurring before day 100 after transplantation, and chronic GVHD was defined as any GVHD occurring after day 100. It is now recognized that typical features of chronic GVHD can occur before day 100 and that typical features of acute GVHD can occur after day 100. Acute and chronic GVHD are no longer defined by their time of onset but rather by their clinical features.

Acute graft-versus-host disease

Acute GVHD can affect the skin, gut, and/or liver. Acute GVHD of the skin most commonly manifests as an erythematous macular rash. The rash may progress to a confluent rash, generalized erythroderma, and blistering of the skin similar to a severe burn. GI involvement typically causes diarrhea with crampy abdominal pain but may also cause loss of appetite, nausea, and vomiting if there is upper GI involvement. Hepatic involvement may lead to hyperbilirubinemia, transaminitis, and progressive liver failure. Acute GVHD is graded by the extent of skin rash, the amount of diarrhea, and the degree of bilirubin elevation according to the Glucksberg or the modified Keystone criteria. Because of the challenges in interobserver and cross-institutional agreement when staging GVHD, further attempts to standardize GVHD data collection and better support interventional studies, such as described by the MAGIC group, have been reported. This system classifies symptoms more quantitatively and categorizes biopsies (non-GVHD, nondiagnostic, equivocal, and positive) to increase consistency across transplant centers. Patients with grade I disease have skin disease <50% BSA and a milder course. Those with grade II to IV disease have multiorgan disease, and patients with grade III or IV disease have a poor prognosis, with increased mortality rates. Diagnosis depends on clinical presentation in combination with laboratory studies and tissue biopsy showing apoptotic bodies.

Prevention of GVHD is more successful than treatment of GVHD. Commonly used GVHD prophylaxis regimens combine a calcineurin inhibitor (tacrolimus, cyclosporine) with low-dose methotrexate. Because of the renal and mucosal toxicities seen with these regimens, alternative prophylactic regimens are being explored. Sirolimus and mycophenolate mofetil are alternatives to methotrexate to decrease the toxicity of GVHD prophylaxis. The use of posttransplant cyclophosphamide (PT-Cy) is being explored in a randomized study versus tacrolimus/methotrexate in matched donors after encouraging data in the haploidentical population and retrospective analyses.

Other methods to prevent GVHD include depleting the graft of donor T cells, either by an in vitro procedure after procurement of hematopoietic cells or by exposure to T-cell–depleting antibodies such as ATG or alemtuzumab. While these strategies result in a significant reduction in

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022

acute GVHD they can also result in poor engraftment, higher infection rates because of delayed immune reconstitution, posttransplant lymphoproliferative disorders, and increased risk of relapse.

Therapy for higher-grade acute GVHD consists of high-dose corticosteroids, typically 1 to 2 mg/kg/day of methylprednisolone or the equivalent, which are tapered upon obtaining a response. Calcineurin inhibitors are continued or restarted. Sirolimus has a potential role in place of steroids for standard-risk acute GVHD as defined by Minnesota GVHD risk score and Ann Arbor biomarker status (REG-3α and ST2), studied as part of the BMT CTN 1501 trial. Use of the topical GI steroids beclomethasone and budesonide may also be beneficial for patients with upper GI GVHD. Patients not responding to or experiencing recurrence of GVHD on high doses of corticosteroids (considered steroid-refractory) have a poor prognosis with 1-year survival <10% from continued acute GVHD, infection, and chronic GVHD. Second-line agents added in the steroid-refractory setting include ruxolitinib (currently the only FDA-approved medication for acute GVHD), alemtuzumab, ATG, extracorporeal photopheresis, mycophenolate mofetil, pentostatin, basiliximab, infliximab, and etanercept. Ruxolitinib at a dose of 10mg twice daily was found in a randomized study in steroid-refractory acute GVHD versus investigator's choice to lead to a 62% Overall Response Rate (ORR) compared to 39% ($P < 0.001$). Given the paucity of proven effective options for steroid-refractory GVHD, patients with GVHD should be encouraged to participate in clinical trials.

Chronic graft-versus-host disease

Chronic GVHD affects long-term survivors of allogeneic HCT and can lead to long-term morbidity, disability, and diminished quality of life. Chronic GVHD is a distinct disorder in which the manifestations often resemble those seen in spontaneously occurring autoimmune disorders. The diversity of the manifestations limited clinical study of chronic GVHD and led to the creation of a National Institutes of Health (NIH) consensus project to produce working definitions for clinical and pathologic diagnosis, staging, and response criteria, as well as suggestions for supportive care, clinical trial design, and biomarkers. In the NIH scoring system, chronic GVHD is classified as mild, moderate, or severe based on the number of organs involved and the extent of involvement within each organ.

An overlap syndrome of acute GVHD can be found in patients with chronic GVHD, where clinical manifestations of both disorders present concurrently. Diagnostic features of chronic GVHD are summarized in Table 14-6.

The greatest risk factor for development of chronic GVHD is prior acute GVHD, so it is seen more often in patients receiving peripheral blood as an HPC source and less often following the use of PT-Cy. Therapy in patients with chronic GVHD begins with corticosteroid monotherapy after a report by the Seattle transplant group showing monotherapy is more effective than in combination with azathioprine. A study comparing cyclosporine plus prednisone therapy with prednisone was also unable to show a benefit to combination therapy. Ruxolitinib was shown to have activity in cGVH and ibrutinib, the first FDA-approved agent for GVHD, achieved this designation by demonstrating benefit for the treatment of steroid-refractory cGVH. Later, belumosudil, a rho-associated coiled-coil-containing protein kinase-2 (ROCK2) inhibitor, was also approved for cGVHD after showing benefit in patients with 2-5 prior lines of therapy. The overall response rate was 74%, with responses seen in all affected organs and a median duration of response of 54 weeks. Other therapies currently used but not supported by randomized trials or FDA approval include psoralen plus ultraviolet A, extracorporeal photopheresis, pentostatin, imatinib, and rituximab.

The major cause of death in patients with chronic GVHD is infection from the profound immunodeficiency associated with chronic GVHD and its therapy. Careful monitoring with antibiotic prophylaxis for encapsulated bacteria (penicillin VK) is warranted in all patients. Patients with frequent infections and immunoglobulin levels <400 may benefit from intravenous immunoglobulin replacement. Patients should remain on prophylaxis for viruses, *P. jirovecii* pneumonia, and fungal infections (yeasts and molds).

CAR T–related complications

Cytokine release syndrome and neurotoxicity

Adoptive cell therapy with CAR T cells is associated with unique toxicities, which can be severe or even fatal. For CD19-directed therapy, common side effects include CRS, neurological toxicity, and B-cell aplasia. CRS is a systemic inflammatory response that follows the infusion of the CAR T-cell product and is characterized by systemic symptoms which are mild in most, but severe and life-threatening in some patients. It is felt to be the result of cytokines such as IFN-γ, TNF-α, and IL-6 released from activated lymphocytes and/or other immune cells during the antitumor response and rapid CAR T-cell activation and expansion. This systemic inflammatory disorder ranges in severity from low-grade constitutional symptoms, such as fever and flu-like symptoms, to a high-grade syndrome associated with hypotension, lung injury,

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022

Table 14-6 Signs and symptoms of chronic GVHD

Body site	Diagnostic of chronic GVHD	Distinctive in chronic GVHD but not diagnostic	Other features*	Common to both acute and chronic GVHD
Skin	Poikiloderma Lichen planus–like sclerosis Morphea-like features Lichen sclerosis–like features	Depigmentation	Sweat impairment Ichthyosis Keratosis pilaris Hypopigmentation Hyperpigmentation	Erythema Maculopapular rash Pruritus
Nails		Dystrophy Ridging Splitting Brittleness Onycholysis Pterygium unguis Nail loss†		
Scalp and body hair		Scarring/nonscarring scalp alopecia Scaling Papulosquamous lesions	Thinning scalp hair Premature graying	
Mouth	Lichen-type features Hyperkeratotic plaques Restriction of mouth opening from sclerosis	Xerostomia Mucocele Mucosal atrophy Pseudomembranes† Ulcers†		Gingivitis, mucositis Erythema Pain Food sensitivities
Eyes		Dry, gritty, or painful eyes† Cicatricial conjunctivitis Keratoconjunctivitis sicca† Confluent areas of punctate keratopathy	Photophobia Periorbital hyperpigmentation Blepharitis	
Genitalia	Lichen planus–like vaginal scarring or stenosis	Erosions† Fissures† Ulcers†		
GI tract	Esophageal web Strictures or stenosis in the upper to mid-third of the esophagus†		Exocrine pancreatic insufficiency	Anorexia Nausea Vomiting Diarrhea Weight loss
Liver				Total bilirubin, alkaline phosphatase >2-3 × upper limit of normal† ALT or AST >2-3 × upper limit of normal†
Lung	BOS diagnosed with lung biopsy‡	BOS diagnosed with PFTs and radiology†		
Muscles, fascia, joints	Fasciitis Joint stiffness or contractures secondary to sclerosis	Myositis/polymyositis†	Edema Muscle cramps Arthralgia or arthritis	
Hematopoietic and immune			Thrombocytopenia Eosinophilia Lymphopenia Hypo- or hypergammaglobulinemia Autoantibodies (AIHA and ITP)	

Table continues on next page

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022

Table 14-6 Signs and symptoms of chronic GVHD *(continued)*

Body site	Diagnostic of chronic GVHD	Distinctive in chronic GVHD but not diagnostic	Other features*	Common to both acute and chronic GVHD
Other			Pericardial or pleural effusions Ascites Peripheral neuropathy Nephrotic syndrome Myasthenia gravis Cardiac conduction abnormality Cardiomyopathy	

Adapted from Filipovich AH et al, *Biol Blood Marrow Transplant*. 2005;11:945-956 (© 2005), with permission from Elsevier.

AIHA, autoimmune hemolytic anemia; BOS, bronchiolitis obliterans syndrome; ITP, immune thrombocytopenic purpura; PFT, pulmonary function test.

*Can be acknowledged as part of the chronic GVHD symptomatology if the diagnosis is confirmed.

†In all cases, infection, drug effects, malignancy, or other causes must be excluded.

‡Diagnosis of chronic GVHD requires biopsy or radiology confirmation (or Schirmer test for eyes).

and life-threatening multiorgan dysfunction. Fulminant macrophage activation syndrome or hemophagocytic lymphohistiocytosis may occur. Treatment of CRS is primarily symptomatic/supportive and may include the use of vasopressors, blood product transfusions, and mechanical ventilation. The IL-6 receptor antagonist antibody tocilizumab can abrogate CRS without interfering with the antitumor response, whereas systemic corticosteroids, while also effective for the treatment of CRS, may interfere with the antitumor activity of CAR T cells. Because of the use of diverse grading systems for CRS and neurotoxicity across clinical trials, in 2018 the American Society of Transplantation and Cell Therapy published consensus definitions and grading systems for both CRS and neurotoxicity. In this new system, CRS grading is based on the presence of fever and dependent on the degree of hypoxia and hypotension that occurs. Neurotoxicity is now termed *immune effector cell–associated neurotoxicity syndrome* (ICANS), with the grading dependent on the presence of neurological findings and ability to answer questions as part of a new immune effector cell associated encephalopathy score. ICANS can manifest as delirium, dysphasia, akinetic mutism, and seizures, and is the second most common side effect of CAR T-cell therapy occurring concurrently with or after CRS. Its presentation can range from headache, aphasia, tremor, or more serious complications, such as seizure, somnolence, and cerebral edema which can be life-threatening. While largely reversible, fatal cases of cerebral edema have occurred. The mechanism of ICANS is unclear and while certain predictors such as high tumor burden and increased depth of lymphodepletion correlate with higher rates of neurotoxicity, these complications remain difficult to predict. While CRS and ICANS are potential complications of CAR T-cell therapy, they are generally felt to be reversible toxicities with low risk of treatment-related mortality. In fact, the TRM of CAR T-cell therapy from large clinical trials is within a similar range to patients undergoing autologous transplant, the alternative treatment option available.

Late effects

As the number of long-term survivors following HCT increases, the need for understanding late side effects of HCT is essential both for the care of the survivors and to anticipate the needs of the group as a whole. Joint guidelines from the European Group for Blood and Marrow Transplantation (EBMT), CIBMTR, and American Society for Transplantation and Cellular Therapy (ASTCT) recommend at least annual evaluation of long-term survivors to monitor for late effects and preventive health screening.

Endocrine adverse effects

Endocrine sequelae of myeloablative transplantation may be significant, especially in children, as CyTBI leads to growth hormone deficiency in 20% to 70% of children. In addition, many patients of all ages develop thyroid dysfunction, often compounded by the effects of therapy before transplantation. Gonadal tissue damage is common and may result in delayed or absent development of secondary sexual characteristics with the need for sex hormone replacement. The risk for gonadal damage appears to depend on multiple factors, including age, sex, type of transplantation, previous therapy, and conditioning regimen. For many young adults, there is a high risk of infertility after HCT and counseling for sperm or egg banking should be discussed with young patients before HCT. One study of 39 male patients evaluated after HCT demonstrated spermatogenesis in only 28% of the patients. Factors associated with sperm production were age >25

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022

years at transplantation, longer interval from transplantation, and no chronic GVHD. For many patients, the course of their disease does not allow for preservation of gametes; however, counseling with fertility specialists after transplant may allow options in the future.

Iron overload

Patients undergoing transplant for a hematologic disorder are often transfused heavily before HCT and continue to require transfusions in the peri-transplantation period. Following hematopoietic recovery, phlebotomy or chelation therapy to target a ferritin at least below 300 ng/mL can help prevent long-term sequelae of iron overload.

Musculoskeletal complications

Patients receiving high-dose corticosteroids for their underlying disease or for GVHD have an increased risk of avascular necrosis of the bone, loss of bone density, and myopathies. Avascular necrosis of the bone can cause progressive collapse of the femoral head, humeral head, and other bones and typically occurs in adolescent and young adult patients treated with corticosteroids. Avascular necrosis is a major cause of morbidity in this age group and frequently leads to intractable pain and loss of mobility, requiring joint replacement at a young age. Osteoporosis resulting from steroid use and therapy-induced menopause is common. All patients should obtain bone densitometry at 1 year after transplantation and as needed afterwards. Vitamin D deficiency is common, and attention to supplementation of vitamin D may help limit loss of bone density.

Secondary malignancies and posttransplantation lymphoproliferative disorders

Survivors of allogeneic HCT are at increased risk for a variety of second malignancies, including a 2- to 3-fold increased risk of solid tumors compared with their age-matched controls. The risk increases over time after transplantation, with greater risk among younger patients. In a retrospective multicenter study that included approximately 20,000 patients who had received either allogeneic or syngeneic transplantations, the cumulative incidence rates for the development of a new solid cancer were 2.2% and 6.7% at 10 and 15 years, respectively. The risk was significantly elevated for cancers of the buccal cavity, liver, brain, bone, and connective tissue, as well as malignant melanoma. Higher doses of TBI were associated with a higher risk of solid cancers. Patients should be instructed to avoid ultraviolet exposures and to use sunscreens and protective clothing. Dermatologic consultation for close monitoring for and management of skin cancers in high-risk patients should be employed.

PTLDs after allogeneic HCT are usually related to EBV reactivation and complicate approximately 2% to 4% of allogeneic HCTs. They occur more commonly with T-cell–depleted grafts, transplants with highly immunosuppressive GVHD prophylaxis or treatment regimens, and in recipients >50 years old. PTLD may be polymorphic, consisting of a nonclonal proliferation of B cells, or monomorphic, manifesting as a clonal proliferation of B cells, often large B-cell lymphoma. Treatment consists of reducing and eliminating immunosuppression, monoclonal antibody therapy with rituximab, donor leukocyte infusions and, in the case of aggressive or unresponsive lymphomas, chemotherapy. EBV-specific cytotoxic T cells have the potential to improve outcomes of PTLD and are in development.

Palliative care and mental health

Because of the significant symptom burden seen in patients during the peritransplant period, interventions to improve control can have major benefits to patients and caregivers. HCT recipients have significant physical symptoms that usually begin soon after conditioning chemotherapy and continue throughout the peritransplant period. In addition, the associated physical isolation and prolonged hospitalization contributes to a reduction in quality of life and mood. The psychological impact of a recipient's transplant experience can impact transplant-related outcomes months and years later, and in others contributes to the development of posttraumatic stress disorder (PTSD) and depression. Concurrent conditions such as chronic GVHD that impacts body image and function, as well as the corticosteroids used to treat the condition can increase the risk further. For this reason, many centers are incorporating early palliative care consultation into the care of their HCT recipients to better control both physical symptoms and to increase psychological support. This intervention is supported by a randomized multicenter trial that showed an improvement in depression (-1.21, $P = 0.02$) and PTSD (-1.63, $P = 0.027$) at 6 months posttransplant.

Post-HCT relapse and maintenance

Relapse is the major cause of treatment failure after autologous HCT and is common after allogeneic HCT. In the setting of autologous HCT, intrinsic disease resistance to chemotherapy and/or radiation, involvement of sanctuary sites with reduced chemotherapy exposure, such as the CNS, and the existence of cancer stem cells that may be quiescent and therefore more resistant to the effects of high-dose chemotherapy and radiation may account for relapse. Maintenance therapies after autologous HCT predictably prolong the time to progression at the expense of ongoing treatment and may improve OS in select diseases (eg,

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022

lenalidomide in multiple myeloma), but no maintenance therapy to date has been demonstrated to improve the curative potential of autologous HCT. Other examples of maintenance in the autologous setting include brentuximab for high-risk HL and rituximab for mantle cell lymphoma.

Even with the benefit of the GVT effect, attempts to reduce relapse with the use of posttransplant maintenance therapy in allogeneic recipients have been investigated. While initial studies on the use of hypomethylating agents post-HCT have not shown clear benefit, studies using FLT3 inhibitors post-HCT have suggested improvement in outcomes. Studies to clarify this question include the BMT CTN 1506 trial, which randomized patients with $FLT3^{mut}$ AML to gilteritinib versus placebo. The trial is now closed to accrual and results are pending.

Cells to prevent or treat relapse after allogeneic stem cell transplantation

Definitive evidence for a GVT effect comes from the use of donor lymphocyte infusions (DLIs). DLI confers a direct graft-versus-malignancy effect by infusion of alloreactive donor lymphocytes, typically in the absence of immune suppression that would prevent GVHD. Purposes of DLI include conversion of mixed-donor chimerism to full-donor chimerism after HCT, as preemptive therapy to prevent relapse, or for the treatment of relapse. Preemptive or prophylactic DLI has been attempted, but no large prospective trials have been performed.

The application of DLI is not without toxicity and can carry a mortality rate of 3% to 10%, with acute GVHD and marrow aplasia being the leading causes of death. The incidence of severe acute and chronic GVHD after DLI is ~50%, with more than half of the patients who develop chronic GVHD having extensive disease. The onset of acute GVHD typically occurs 32 to 42 days after DLI. To avoid this risk of GVHD, other posttransplant cellular therapies such as CAR T are being explored in the postallogeneic setting as discussed in this chapter. Consideration is given to a second allogeneic HCT in some instances, though data are very limited to estimate efficacy versus DLI, and it is unclear whether the same donor or a different donor is preferable.

Disease-specific indications for HCT and cellular therapy

Acute myeloid leukemia

The most prevalent adult indication for allogeneic HCT is AML. The decision to use allogeneic transplant as a consolidative strategy in AML is guided by 2 major disease-specific factors, namely genomic characteristics at diagnosis and depth of remission. A meta-analysis of 24 trials comprising 6007 patients suggested a survival benefit of allogeneic HCT compared with contemporaneous chemotherapy in both poor-risk and intermediate-risk AML. The revised 2017 European Leukemia Network (ELN) criteria have incorporated a number of gene mutations including *TP53*, *ASXL1*, and *RUNX1*, and includes quantitative data on the allelic ratio of *FLT3*-ITD, as well as concurrent mutations in the case of *FLT3*-ITD and NPM1 to parse out patients who are more likely to benefit from this intervention in CR1. Studies have shown that patients with measurable residual disease at the time of transplant have higher post-HCT relapse than those without, at a rate of 65% versus 18%, respectively, although the prospective utility of MRD in clinical decision-making is still being clarified.

A CIBMTR prospective cohort study enrolling 1483 patients from 2009 to 2011 found significantly improved OS and PFS with the use of IV busulfan-based conditioning relative to TBI-based conditioning with a significant 2-year OS benefit in AML (57% versus 46%, $P = 0.003$). As such, IV busulfan-based conditioning has become standard at many transplant centers. A nationwide randomized phase 3 trial comparing MAC versus RIC transplantation in younger patients with MDS and AML (BMT CTN 0901) failed to show a significant OS difference, with a higher relapse rate in RIC being offset by significantly higher treatment-related mortality with MAC. In younger, fit patients with a high likelihood of relapse, it is intuitive to escalate the potency of the preparative regimen.

Autologous transplant in AML may have some renewed interest as a consolidative strategy when guided by MRD data in low or intermediate-risk disease AML but for high-risk disease, is inferior to allogeneic transplant.

Outcomes of allogeneic HCT in CR1 are predictably better than in CR2 or higher, or with refractory AML. Survival after allogeneic HCT is approximately 40% to 60% in CR1, ~25% to 30% in CR2, and ~10% in refractory AML. A CIBMTR study established a predictive score for survival in refractory AML based on CR1 duration <6 months, presence of circulating blasts, donor other than HLA-matched sibling, Karnofsky performance status (KPS) <90, and poor-risk cytogenetics. The authors found a 3-year OS of 19% in the entire AML cohort, but a 3-year OS of 42% in those with a risk score of 0.

Ongoing challenges remain in high-risk genomic subsets, including *TP53*-mutated AML, where relapse risk has not been as responsive to HCT. Some areas of development to mitigate relapse risk include the use of posttransplant hypomethylating agents or targeted therapies including *FLT3* inhibitors.

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022

Newly diagnosed acute promyelocytic leukemia (AML FAB M3) has cure rates in excess of 80% with the all-transretinoic acid in combination with chemotherapy or arsenic trioxide. For patients who relapse, salvage therapy is based on prior therapies and duration of remission . Consolidation with autologous or allogeneic HCT is required to maximize cure rates in these patients. For patients in molecular remission (lacking detectable PML-RAR1 fusion transcript), autologous HCT offers similar Disease-Free Survival (DFS) to allogeneic HCT but with significantly superior 5- or 7-year OS of 60% to 75% for autologous HCT versus 50% to 52% with allogeneic HCT. For those patients with detectable disease after salvage chemotherapy or relapsing after autologous HCT, allogeneic HCT offers the best opportunity for long-term survival.

Acute lymphoblastic leukemia

Several recent therapeutic advances in ALL including the extension of pediatric regimens to young adults and incorporation of bispecific T-cell engagers and tyrosine kinase inhibitors to deepen responses have diminished the number of patents relegated to allogeneic transplant in first remission. High-risk patients are typically identified based on MRD measurements at completion of induction or consolidation therapy. Other disease characteristics including Ph-like gene expression profiles and the early T-cell precursor immunophenotype are important considerations in the transplant decision.

Ph-negative ALL

The largest prospective trial to date addressing the role of allogeneic transplant in Ph-negative ALL is the MRC UKALLXII-ECOG2993 trial, with nearly 2000 newly diagnosed patients from 1993 to 2006, demonstrating a superior 5-year OS in Ph^- ALL patients who underwent allogenic transplant at 53% versus 45%. A meta-analysis of 2962 Ph^- ALL patients from 13 studies also showed superior OS in patients under the age of 35 with a matched sibling donor compared with the no-donor group. However, these and several smaller prospective donor–versus–no-donor comparisons are less relevant since most patients in those studies did not receive aggressive pediatric ALL induction protocols now used in patients up to 40 years of age. This escalation of upfront chemotherapy has, across multiple international trials, improved 5-year survival rates from the 40% to 50% range to the 60% to 70% range, diminishing the role of transplantation. Additional incremental gains have been made by using bispecific T-cell engagers and B-cell antibodies to deepen remissions. An analysis of the GRAALL-2003/2005 studies demonstrated that allogeneic HCT in CR1 only benefited high-risk Ph-negative ALL patients with positive minimal residual disease ($\geq 10^{-3}$) at the end of induction.

Ph-positive ALL

Ph^+ ALL has traditionally lagged behind Ph-ALL in outcomes with a higher risk of relapse resulting in a strong recommendation for transplant. The incorporation of the first Tyrosine Kinase Inhibitor imatinib into chemotherapy was able to increase remission rates allowing more patients to proceed to transplant. A subsequent prospective phase 2 trial (S0805) of dasatinib plus hyperCVAD followed by transplant in younger adults with Ph^+ ALL, demonstrated DFS and OS benefit in patients undergoing allogeneic transplant. Therefore, at this time, for the fit patient with an available donor, allogeneic transplant remains a strong recommendation in CR1. However, this may evolve with the impressive outcomes combining chemotherapy with the second-generation TKIs with a 2-year DFS of 80%. Recent phase 2 data using steroids and dasatinib induction and blinatumomab maintenance reported complete remission rates of over 95% substantiating efforts to deescalate the chemotherapy backbone needed to achieve remission. One third of these patients went onto allogeneic stem cell transplant. The enhanced depth of remission with better TKI and immunotherapies, and the ability to monitor MRD, may obviate transplant in a subset of patients in the future.

Relapsed disease

The ability to bridge patients with relapsed ALL to an allogeneic HCT is improved with the advent of effective immunotherapies therapies including blinatumomab, inotuzumab ozogamicin, and CAR T-cell therapies with response rates of up to 80%. If patients reach allogeneic HCT, long-term survival continues in about 20% to 30% of relapsed/refractory patients.

CD19-targeted CAR T-cell therapy for B-cell ALL

Response rates of approximately 80% to 90% have been reported with CD19-directed CAR T cells in pediatric and adult relapsed ALL. In August 2017, tisagenlecleucel (CTL019), a 41BB, CD3ζ CAR T product became the first CAR T-cell therapy to gain regulatory drug approval by the FDA. Approval was granted based on results from a single-cohort, multicenter global phase 2 trial (ELIANA). Among 75 patients aged 3 to 23 years with relapsed or refractory CD19+ B-ALL who received an infusion of tisagenlecleucel, the overall remission rate was 81% (all measurable residual disease–negative) with 12-month Event-Free Survival (EFS) and OS estimates of 50% and 76%, respectively. Grade 3/4 events suspected to be caused by the CAR

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022

T-cell therapy were noted in 55 of the 75 patients (73%). Of note, 77% of the patients experienced CRS, with 48% of them requiring tocilizumab for management, while 40% experienced neurologic events. While approval for pediatric B-cell ALL came early, to date anti-CD19 CAR T-cell therapy has not been approved in adult patients. This approval has been delayed because of the presence of treatment-related complications, specifically the development of cerebral edema and refractory CRS leading to death in early clinical trials. A team at the University of Pennsylvania, using the CTL019 41BB, CD3z anti-CD19_construct (approved in pediatric ALL), reported a CR rate of 90% and 2-year OS of 73% and 2-year EFS of 49.5% among 20 patients receiving a high dose of CAR T cells in a fractionated dosing schema. Patients who received a high-dose, single infusion of CAR T cells had a high rate of refractory CRS, with 3 of 6 patients dying of treatment-related complications, leading to closure of that arm. ZUMA-3, an international phase 2 study of CD28 CD3z CD19 CAR T cells, reported their outcomes in adult ALL patients leading to the recent FDA approval of the first CAR T-cell therapy in the relapsed/refractory adult ALL population with a black box warning for CRS and neurotoxicity. Among 55 treated patients, the complete response rate was 71% with a median duration of 12.8 months. CRS occurred in 89% (n = 49) of patients with grade 3-4 CRS occurring in 24% (n = 13). There were 2 grade 5 events attributable to sepsis and brain herniation again demonstrating the dangers of these treatments. While these data demonstrate clear efficacy for CAR T-cell therapy in B-cell ALL, relapse and toxicity management remain major barriers to their widespread application. Additionally, a major unanswered question in the field is the role of allogeneic transplant as a consolidative procedure in B-cell ALL patients after CAR T-cell therapy.

Chronic myeloid leukemia

Allogeneic transplantation is much less common for chronic-phase CML since the approval of TKIs. Transplantation for chronic-phase CML patients is considered in rare cases of intolerance or resistance to all TKIs, and guidelines suggest it should be considered after 2 lines of treatment failure, including at least 1 second-generation TKI. Patients with a T315I mutation who relapse should be considered for allogeneic HCT given limited duration of response with ponatinib and lack of alternative effective treatment options. Similarly, for accelerated phase (AP) disease, allogeneic HCT should be considered for poor responders to TKI therapy. All CML patients with myeloid or lymphoid blast phase (BP) disease should proceed to allogeneic HCT if possible, ideally after successful treatment to chronic-phase disease with a TKI, with or without induction chemotherapy appropriate for myeloid or lymphoid blast crisis. Patients with AP or BP CML can achieve a complete cytogenetic remission with TKI therapy, but only a third of cases are associated with long-term PFS. Achievement of chronic-phase disease in AP and BP CML is important for reducing risk of relapse following allogeneic transplant.

For patients with detectable molecular, cytogenetic, or morphologic disease relapse after allogeneic HCT, treatment generally consists of withdrawal of immunosuppression and donor leukocyte infusion with a 65% 5-year survival in relapsed CML in a large EBMT study. Given the strong GVL effect in CML, these strategies can be very effective although they run a high risk of stimulating GVHD. Several studies have used TKI therapy to treat "molecular relapse" posttransplant, with remarkable effect alone or in combination with DLI. The choice of TKI should be guided by results of ABL kinase mutation studies given the reported emergence in some cases of unique clones at relapse. In addition, published and ongoing studies have used TKI prophylactically posttransplant in those cases at very high risk of relapse, such as accelerated and BP CML and Ph^+ ALL.

Chronic lymphocytic leukemia/small lymphocytic lymphoma

Allogeneic HCT remains an appropriate consideration for high-risk chronic lymphocytic leukemia (CLL) with deletion of 17p, p53 mutations or complex karyotypes generally after achieving response to targeted therapies, or relapsed/refractory standard-risk disease. Up to 10% of cases of CLL may develop/present with Richter's transformation and in this scenario, allogeneic transplant in first remission has proven benefit over autologous transplant. Three nonrandomized studies provide evidence favoring the option of allogeneic transplant over nontransplant strategies for relapsed or refractory CLL, however these predate the use of targeted inhibitors. Given that BTK and bcl2 inhibitors can overcome the deleterious effects of del17p and new combination therapies of venetoclax and novel antibodies are resulting in undetectable MRD, the role of allogeneic transplant in CLL must be carefully evaluated in older patients where depth and duration of remission may not be as important as quality of life.

RIC has largely supplanted myeloablative approaches, which had a very high NRM of >50%, likely because of the cumulative effects of chemotherapy as well as the older age of the CLL population. Preparative regimens differ, but generally they are based on fludarabine-containing regimens, some with low-dose TBI. The ASTCT

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022

consensus on CLL allotransplant recommends monitoring of pre- and posttransplant MRD levels. Long-term outcomes of patients allografted in the German CLL3X trial showed that MRD clearance 1 year after allogeneic transplant resulted in an 87% probability of 10-year DFS.

CD19-targeted CAR T-cell immunotherapy for CLL demonstrated overall response rates of 44% and median OS of 64 months in patients with R/R CLL resistant to ibrutinib and venetoclax in a phase 2 study. Further long-term outcome data will help determine how to position CAR T cells with respect to allogeneic transplant and other therapies in patients with CLL.

Myelodysplastic syndrome

Allogeneic HCT is the only curative therapy for myelodysplastic syndrome (MDS). The challenge in this group of heterogenous diseases is the identification of high-risk patients at presentation as well as evolution of disease in lower-risk patients. The revised International Prognostic Scoring System (IPSS) classifies patients based on degree of cytopenias, karyotype, and percentage of blasts with 5-year survival ranging anywhere from 25% to 75%. There are at least 5 somatic mutations (*RUNX1*, *TP53*, *ETV6*, *EZH2*, *ASXL*) that have additive prognostic benefit to the IPSS-R scoring system and should be considered in the transplant decision. There is increasing recognition of a subset of patients with germline mutations in *DDX41*, *RUNX1*, or *GATA2* that predispose to MDS, may present at a younger age, and require special consideration of use of a familial donor.

Based on decision analysis, allogeneic HCT is indicated for all transplant-eligible patients with IPSS-R intermediate-, high-, or very high-risk disease. Importantly, patients with lower-risk disease should be monitored for evolution including worsening of cytopenias, increasing blast percentage and new cytogenetic abnormalities to ensure timely transplantation before complications related to cytopenias, transfusions associated iron overload, or progression to AML that may delay or preclude transplantation.

An important peritransplant variable to predict risk of relapse in MDS is the percentage of blasts at the time of transplant. Retrospective studies have compared intensive induction chemotherapy to hypomethylating treatment showing no benefit to intensive chemotherapy for cytoreduction. In patients with over 10% blasts, hypomethylating therapy as a bridge to transplant is generally undertaken. Lastly MRD remains an important predictor of relapse similar to the case in AML. Data in p53-mutated MDS suggests a lower relapse risk in patients who achieve MRD negative state prior to transplant. Several strategies are being explored to increase depth of remission prior to transplant including the use of CPX-351, shown to be effective in secondary AML, as well as combinations of venetoclax with hypomethylating agents, and lastly post-transplant strategies including combinations of hypomethylating agents and DLI for molecular relapse.

Follicular lymphoma

Follicular lymphoma (FL) typically runs an indolent course but is incurable with conventional chemotherapy. Frontline therapy can lead to prolonged remissions and HCT (either autologous or allogeneic) is reserved for patients with relapsed disease. Nonrandomized retrospective studies, including studies from the German Low-Grade Lymphoma Study Group and the National LymphoCare Study/CIBMTR have suggested a survival benefit for autologous transplantation in patients with early progression of FL within 2 years of frontline therapy.

Several nonrandomized studies showed lower relapse rates after allografting compared with autologous HCT, but this gain was offset by the considerably higher NRM with MAC conditioning. RIC allogeneic transplants have been used in FL, including cases failing an autologous transplant. Two prospective studies have used fludarabine-based RIC conditioning regimens. The University of Texas MD Anderson Cancer Center reported 6-year PFS and OS rates of 83% and 85%, respectively, with a NRM of 15% while a Cancer and Leukemia Group B trial reported 2-year PFS and OS rates of 71% and 76%, respectively, with an NRM of only 7%. Chemotherapy-sensitive disease before transplantation predicted superior outcomes. The EBMT performed a retrospective analysis comparing autologous (n = 726) to RIC allogeneic HCT (n = 149) as first-transplant strategy in relapsed FL. Relative to autologous HCT, RIC allogeneic HCT yielded significantly reduced relapse rates and longer PFS at the expense of increased NRM leading to equivalent 5-year OS (72% autologous transplant versus 69% allogeneic HCT, P = not significant). Based on lack of superiority in overall survival, allogeneic transplantation should be reserved for selected patients with relapse postautologous HCT.

The incidence of transformation from FL to diffuse large B-cell lymphoma is ~3% per year. Transformed FL may represent a unique situation where autologous transplant could be a consideration in first remission to prolong duration of remission recently demonstrated in a matched propensity score analysis.

Anti-CD19 CAR T cells are now also FDA-approved in chemorefractory FL that has progressed after at least 2 prior lines of treatment following data from the phase 2 ZUMA-5 clinical trial which demonstrated an overall response rate of 91% in patients with a CR rate of 61%. 74% of patients remained in remission at 18 months. These

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022

excellent results are tempered by the presence of grade 3+ CRS and neurotoxicity which occurred in 8% and 21% of patients, respectively.

Diffuse large B-cell lymphoma

The majority of patients with aggressive and very aggressive B-cell NHLs can be cured with frontline chemoimmunotherapy, with or without consolidative radiotherapy. A retrospective analysis of SWOG 9704 demonstrated PFS and OS benefit with autologous HCT in International Prognostic Index (IPI) high-risk Diffuse Large B Cell Lymphoma (DLBCL). As it stands, upfront autologous HCT for DLBCL in CR1 should be reserved for rare, high-risk patients, ideally within the context of a clinical trial.

For patients who fail to achieve CR with initial therapy or relapse after a brief CR duration, only 30% to 40% will respond to salvage chemotherapy and may subsequently undergo consolidation with autologous HCT. The multicenter, prospective PARMA trial established the role of autologous HCT for patients with relapsed, chemotherapy-sensitive DLBCL with superior 5-year EFS and OS of 46% and 53%, respectively, for the transplantation arm and 12% and 32%, respectively, for the chemotherapy arm. The subsequent CORAL study established that choice of salvage regimen did not affect outcomes of autologous transplant and maintenance rituximab following transplant did not add any therapeutic benefit. Patients with relapsed DLBCL who were chemotherapy-sensitive unequivocally fared better compared with patients with chemotherapy-resistant disease.

Patients with DLBCL who demonstrate primary refractory disease or relapsed disease that is not responsive to salvage chemotherapy continue to have poor outcomes even after high-dose therapy with autologous HCT. The recent SCHOLAR-1 study reported an ORR of 26% to the next line of therapy and pooled median OS of 6.3 months, indicating a continued therapeutic need. This may be amenable to allogeneic transplant or CAR T-cell therapies

Allogeneic HCT is not offered routinely to patients with DLBCL. Exceptions include select young patients with advanced disease, patients who failed to mobilize adequate CD34+ hematopoietic cells, or patients who failed a previous autologous HCT. In a review of 101 patients with DLBCL who failed an autologous transplant, 3-year NRM was 28% (higher in MAC versus RIC), relapse was 30%, and OS 52%. Time to relapse of <12 months and chemotherapy-refractory disease portended a worse outcome.

CD19-targeted CAR T-cell therapy in DLBCL

In October 2017, axicabtagene ciloleucel (axi-cel) became the second approved CAR T-cell therapy. The drug gained FDA approval for the treatment of adults with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from FL. Approval was granted based on results from a single-cohort, multicenter phase 2 trial (ZUMA-1). In this study, 101 patients (of 111 enrolled) ages 23 to 76 years with histologically confirmed relapsed or refractory large B-cell lymphoma received a target dose of 2×10^6 CAR T cells/kg body weight after undergoing lymphodepleting chemotherapy with low-dose cyclophosphamide and fludarabine. The overall response rate was 82%, with a complete response rate of 54% and median duration of response of 8.1 months. OS was estimated at 52% at 18 months for patients receiving CAR T cells. Neutropenia, anemia, and thrombocytopenia emerged as the most common grade 3 or higher events. CRS and neurologic events occurred in 93% and 64% (grade 3 or higher in 13% and 28%) of the patients, respectively.

Two other forms of CD19 targeted CAR T-cell therapy are approved for relapsed/refractory aggressive B-cell lymphomas. Tisagenlecleucel is also approved for large B-cell lymphoma including DLBCL, high-grade B-cell lymphoma, and DLBCL arising from FL after 2 or more lines of systemic chemotherapy. Unlike the axi-cel, this CAR has a different costimulatory domain with a 41BB activation versus CD28. The pivotal JULIET trial leading to approval was a phase 2, single-arm study involving 93 patients. The best overall response rate was 52% with 40% achieving a complete response. CRS measured using the University of Pennsylvania grading scale demonstrated grade 3-4 CRS in about 22% of patients with no deaths attributed to treatment. Grade 3-4 neurological events occurred in 12% of patients. Lisocabtagene maraleucel is a third product now approved for relapsed, refractory large B-cell lymphoma. Similar to tisagenlecleucel, this is an anti-CD19, 41BB CAR T-cell product. Uniquely it is administered as 2 doses with a fixed ratio of CD4+ and CD8+ CAR T cells. Among 256 evaluable patients treated on a pivotal single-arm clinical trial, the overall response rate was 73% with a complete response in 53% of patients. Grade 3-4 CRS and neurological events occurred in 2% and 10% of patients, respectively.

Future CARs in B-cell malignancies

While clinical data are most mature with CD19-directed CAR T-cell therapy, an increasing number of other antigen targets are being pursued as well (eg, CD20, CD22, CD30 among others). In addition, combinatorial CARs targeting >1 antigen simultaneously are under active development.

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022

Among the most promising strategies, has been the targeting of CD22. The CD22 molecule is restricted to the B-cell lineage and when engaged normally functions to inhibit B-cell signaling. The National Cancer Institute (NCI) reported their outcomes using a 41BB/CD3ζ CAR T-cell product in patients with relapsed B-cell malignancies. Among the 58 patients treated on this early phase trial, the majority had prior exposure to CD19 CAR T cells

(51/58 patients). Despite this the CR rate was impressive at 70% with a median OS of 13.4 months and a median relapse-free survival of 6 months. CRS occurred in the majority of patients, most of it grade 1-2. Hemophagocytosis like manifestations were present in 19/58 (33%) requiring management with anakinra.

Since targeting single antigens with CAR T cells carries the risk of immune escape or loss of the target antigen, a phenomenon well documented in patients treated with CD19-directed CAR T cells, several groups are now promoting dual targeted CAR T-cell approaches. There are several ways to construct a multitargeted CAR T cell with no known superiority to date of one approach to another. Options include (1) generate 2 or more CAR products separately and infuse simultaneously or sequentially; (2) use a bicistronic vector to encode 2 different CARs on the same cell; (3) transduce T cells with more than 1 viral vector each encoding a different CAR (cotransduction); and (4) encode 2 CARs on the same receptor using a single viral vector (tandem). Each approach has is distinct advantages and disadvantages and studies are ongoing evaluating different models of dual or multitargeting CARs. Recently outcomes of a bispecific, tandem anti-CD19/anti-CD20 CAR were reported. At the target dose of $2.5x10^6$ cells/kg, the ORR was 82% and CR rate of 64%. Interestingly, no relapsing patient had documented loss of CD19 suggesting that dual targeted therapy may mitigate one potential mechanism of relapse. Another approach involves dual targeting of CD19 and CD22. AUTO3 is a bicistronic retroviral anti-CD19/anti-CD22 CAR T-cell product given in combination with pembrolizumab. Among 11 patients treated at higher dose levels, the ORR and CR rate were 64% and 55% respectively. Toxicity was limited with no grade 3-4 CRS and only 1 case of grade 3-4 neurotoxicity among 19 evaluable patients. Similarly, Spiegel et al. reported their outcomes with a bispecific tandem CD22-CD19 41BB CAR construct among patients with B-cell ALL and large B-cell lymphoma. Among the B-cell lymphoma patients treated at the recommended phase II dose (n = 15), the ORR was 40% and CR rate was 33%. For patients with B-cell ALL (n = 17), the ORR and CR rates were 100% and 82%, respectively. Unfortunately, despite dual targeting, loss of CD19 occurred among relapsing patients with both B-cell ALL and large cell lymphoma, demonstrating the challenges in mitigating antigen loss as a mechanism of resistance. This represents only a small fraction of the ongoing studies using a multitargeted approach.

Mantle cell lymphoma

Mantle cell lymphoma (MCL) is an uncommon lymphoma (5% to 10% of lymphomas) that generally presents with advanced disease. A small subset presenting with low *SOX11* expression have an indolent course, but in most cases the disease has an aggressive course and is advanced at presentation. High-dose therapy with autologous HCT is typically part of consolidation therapy, yielding 5-year PFS of 50% to 70% and 5-year OS of 60% to 70%, although late relapses are reported. Rituximab maintenance after frontline autologous HCT for MCL maintenance versus observation showed improved EFS and OS in prospective clinical trials. A randomized comparison of autologous transplant versus maintenance rituximab following high-dose induction chemotherapy is still wanting in the field.

For patients with relapsed or refractory disease after autologous HCT, allogeneic HCT is indicated as it offers the only chance for cure and long-term survival. Myeloablative allogeneic HCT can induce durable remissions in MCL, even in heavily pretreated patients, but is associated with significant TRM and morbidity. RIC regimens reduce toxicity without significantly sacrificing curative potential, yielding EFS rates ranging from 50% to 85% even in patients who failed a prior autologous HCT. The main predictors of allotransplant success are chemosensitive disease at the time of transplant and duration of remission following autologous transplant. *TP53* mutation status is important to assess as its negative prognostic impact cannot be overcome even with transplant; these patents may be better served on a clinical trial.

CD19-targeted CAR T-cell therapy in B-cell MCL

Brexucabtagene autoleucel is a CAR product identical to axi-cel but manufactured under different conditions to reduce the burden of malignant CD19 expressing B cells and improve the manufacturing process. This product was tested in relapsed, refractory MCL patients that had progressed after up to 5 prior lines of therapy. The lymphodepletion regimen and cell dose were identical to axi-cel ($2x10^6$ CAR+ cells/kg). In this phase 2 study, 68 patients received treatment with an ORR of 93% and a CR rate of 67%. The 12-month PFS was 61% and 12-month OS was 83%. Grade 3 or higher CRS occurred in 15% and grade 3 or higher neurotoxicity in 31% of patients. Two

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavrillaki on 10 December 2022

fatal infectious adverse events occurred. These data led to FDA approval of brexucabtagene in relapsed, refractory MCL.

Hodgkin lymphoma

Frontline therapy for classical has high cure rates. For patients with relapsed or refractory HL, high-dose therapy with autologous HCT is the standard of care and confers cure rates of 40% to 60% in patients with relapsed, chemotherapy-sensitive disease and 25% to 40% in patients with chemotherapy-refractory disease. Maintenance therapy after autologous HCT has also been evaluated for classical HL. Brentuximab vedotin (BV), an antibody-drug conjugate targeting surface CD30, was evaluated as a maintenance therapy in the AETHERA randomized, placebo-controlled phase 3 study comparing 16 BV treatments after autologous HCT to placebo for classical HL at high risk for relapse or progression. The results demonstrated superior PFS (HR 0.57, $P = 0.001$) with BV but at the expense of increased sensory and motor neuropathy, neutropenia, and 2 cases of fatal acute respiratory distress syndrome attributable to BV.

The role of allogeneic HCT in classical HL is less established and generally pursued only in patients who have persistent marrow involvement, refractory disease, or relapsed or progressive disease after an autologous HCT. In general, RIC transplant regimens are preferred to a fully myeloablative regimen because of a more favorable NRM. The Gruppo Italiano retrospectively compared nearly 200 classical HL cases following autologous transplant and divided the patients into those with a donor (sibling, unrelated, or haploidentical) versus those who could not secure a donor, with the intent that those with donor would have an RIC allogeneic HCT. The 2-year PFS and OS were superior in the donor group (39% versus 14% and 66% versus 42%, respectively). The Seattle group compared the outcome for HLA-matched, unrelated matched, and haploidentical donors in RIC allogeneic HCTs and found survival to be similar in all approaches, with OS of ~60%, and PFS of ~40%. Chemosensitivity before RIC allogeneic HCT predicts reduced risk of relapse.

CD30 CAR T cells in Hodgkin lymphoma

While CAR T-cell therapies in HL are not as advanced as in B-cell NHL, recent data has demonstrated promising outcomes targeting the CD30 antigen. CD30 is a transmembrane receptor overexpressed on Reed-Sternberg cells making it an ideal target for CAR based therapies. One group recently reported their outcomes with anti-CD30 CAR T cells generated using a gammaretroviral vector and CD28 as the costimulatory signaling molecule. In total 41 patients with HL were treated with a median of 7 prior lines of therapy. CRS occurred in 10 patients, all of which were grade 1 with no neurological toxicities reported. The ORR was highest among patients who received a fludarabine-based lymphodepletion regimen (n=32) at 72% with 59% achieving a CR. The 1-year PFS for all patients was 36%. These data provide proof-of-concept for activity of CAR T cells redirected at novel antigens in HL. Further research and clinical trials are indicated before these treatments become mainstream.

Peripheral T-cell lymphoma

Peripheral T-cell lymphomas (PTCLs) account for 10% of NHLs, and their heterogeneity is reflected in the International T-cell Lymphoma Project outcome data. Six prospective nonrandomized studies have examined autologous transplant and found that early transplantation appears to improve outcomes in chemotherapy-sensitive PTCL with 2-year PFS and OS rates of 63.4% and 75.3% in patients who underwent an autologous HCT in CR1 compared with 19.5% and 41.9% in patients not achieving CR1. IPI risk group can also guide transplant selection.

For relapsed or refractory disease, autologous HCT yields 5-year survival rates of about 40% in chemosensitive disease, with similar outcomes observed for allogeneic HCT with MAC or RIC conditioning.

Plasma cell dyscrasias

Multiple myeloma is the most common adult indication for autologous HCT. Compared to chemotherapy, high-dose melphalan therapy with autologous HCT has demonstrated higher response rates and improved PFS and OS across multiple clinical trials. This benefit persists in the era of immunomodulators and proteasome inhibitors. The optimal timing of transplant is contentious in light of very deep responses with novel agents in combination regimens. The IFM 2009 phase 3 randomized study compared initial therapy with lenalidomide, bortezomib, and dexamethasone with or without high-dose melphalan with autologous HCT in untreated MM. Transplantation significantly improved PFS, but there was no difference in OS. A unique consideration in MM is that up to 40% of patients have renal insufficiency and, unlike other hematological malignancies, this does not preclude transplant, although lower doses of melphalan are routinely used.

The utility of tandem transplantation is largely historical. A meta-analysis of 6 randomized trials with ~1000 patients concluded that tandem autologous HCT confers higher response rates compared with single autologous HCT but did not find conclusive evidence for improvement in PFS

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022

or OS. At this time, single autologous HCT after response to primary therapy remains the standard at most institutions. The ASTCT and EBMT recommend allogeneic transplant be considered for patients with early relapse (<24 months) after primary therapy and/or high-risk features (ie, cytogenetics, extramedullary disease, plasma cell leukemia, or high lactate dehydrogenase (LDH)).

MM was the first disease to demonstrate the benefit of maintenance therapy with lenalidomide after autologous HCT, improving median PFS from 23 to 27 months to 47 to 53 months and the median OS from 3 to 5 years to 7 to 10 years. Current research uses immunotherapies, including antibodies (targeting CD38 and B-cell maturation antigen [BCMA]) and CAR T cells, to enhance the depth of remission to MRD negative status and augment the effect of autologous HCT. With a rapidly expanding therapeutic landscape, it is key to understand how to integrate therapies including multidrug induction regimens, the prolonged relapse-free survival offered by autologous stem cell transplant, and potent and well-tolerated bispecific antibodies and CAR T cells.

AL (light chain amyloid) amyloidosis is a clonal plasma cell disorder characterized by tissue deposition of amorphous extracellular material composed in part of immunoglobulin light- or heavy-chain fragments in vital organs, such as the heart, lung, kidney, liver, and CNS. While autologous HCT can reverse the disease process for selected patients, because of preexisting organ dysfunction, the NRM of autologous HCT is 2 to 5 times (NRM ~5% to 10%) higher than for MM (NRM ~2%). Several studies have suggested a 2- to 3-year survival of ~70% after autologous HCT, although patients with multiorgan involvement have inferior survival.

Multiple myeloma CAR T-cell therapy

The B-cell maturation antigen is a member of the tumor necrosis factor superfamily that is expressed by both malignant and normal plasma cells and is a target exploited by CAR T-cell therapies in MM. Several BCMA CAR T-cell products are under investigation, with 1 product approved and additional approvals anticipated within the next 1 to 2 years. Idecabtagene vicleucel (ide-cel) also known as bb2121 is a 41BB, CD3ζ CAR T-cell product targeting BCMA and is the first FDA-approved BCMA CAR product. In a multicenter phase 2 clinical trial of 128 patients with relapsed, refractory MM treated with ide-cel, the ORR was 73% and the CR rate was 33%. MRD negativity was achieved in 26% of patients. As with other CAR T therapies, CRS occurred in 84% with only 5% of patients having grade 3+ toxicities. Neurotoxic effects occurred in 18% of patients. A second product, ciltacabtagene autoleucel, is a CAR T cell that targets 2 epitopes on BCMA. Interim results from their phase 2 clinical trial among 97 patients with relapsed, refractory MM demonstrated an ORR of 94.8% and a stringent CR rate of 56%. The 6-month PFS and OS were 87.4% and 93.8%, respectively. CRS occurred in 95% of patients and neurotoxicity in 21% of patients. To date it remains unclear if CAR T-cell therapies will be curative in MM, with relapse remaining a barrier to the high upfront response rates. In addition to BCMA, several other antigens are under active investigation in MM.

Nonmalignant hematologic diseases

Aplastic anemia and bone marrow failure syndromes

Therapy for aplastic anemia depends on the severity of the aplasia, the availability of an MRD, and the age of the patient. The standard first-line therapy for younger patients with newly diagnosed severe aplastic anemia is allogeneic HCT if a MRD is available. If a MRD is not available or a patient is an older adult, immunosuppressive therapy with equine ATG, cyclosporine and the thrombopoietin receptor agonist eltrombopag is used for initial therapy with unrelated donor transplant reserved for patients who do not adequately respond to immunosuppressive therapy. Long-term survival following an MRD transplant exceeds 80%. Inferior survival is associated with older age, use of an unrelated donor, and prior transfusion. Bone marrow rather than peripheral blood is the preferred source of stem cells to reduce the risk of chronic GVHD. Most centers use high-dose cyclophosphamide with ATG as a preparative regimen, although regimens incorporating fludarabine with ATG and lower doses of cyclophosphamide are also efficacious. For younger patients (often defined as <40 years old) with newly diagnosed idiopathic severe aplastic anemia and an HLA-identical sibling, many centers recommend immediate transplantation to minimize alloantigen sensitization with transfusions, which historically has resulted in an increased risk of graft rejection and poorer outcomes. Secondary malignancies occur after transplantation for severe aplastic anemia in as many as 10% of cases 15 years from transplant.

It is important to assess for Fanconi anemia and dyskeratosis congenita as congenital causes of bone marrow failure in newly diagnosed aplastic anemia patients to help select the appropriate treatment course and ensure any related stem cell donor is screened for the recipient's bone marrow failure syndrome. Patients with Fanconi anemia frequently do not have all of the stigmata of the

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022

disease, and the diagnosis may be overlooked. The sensitivity of patients with Fanconi anemia to alkylating agents is well-described, and transplantation can be successfully performed using nonmyeloablative regimens.

Immune deficiency and inherited metabolic disorders

Many immune deficiency disorders become evident in infancy secondary to an increased rate of infections or the presence of opportunistic infections. The most common diseases for which allogeneic transplantation is indicated include adenosine deaminase deficiency (ADA), SCID, Wiskott-Aldrich syndrome, Nezelof syndrome, Omenn syndrome, MHC antigen deficiency, leukocyte adhesion defect, Chédiak-Higashi syndrome, chronic granulomatous syndrome, and DiGeorge anomaly. Allogeneic HCT is undertaken in these disorders to provide a stable source of immunologically competent cells. The major complications are rejection of the marrow graft and GVHD.

A number of inborn errors of metabolism, including globoid cell leukodystrophy; metachromatic leukodystrophy; adrenoleukodystrophy; mannosidosis; fucosidosis; aspartylglucosaminuria; Hurler, Hunter, Maroteaux-Lamy, and Sly syndromes; and Gaucher disease type III, can be corrected with allogeneic HCT. One of the most important steps is the early identification of the disorder before the development of end-organ damage. In a number of these disorders, allogeneic HCT halts disease progression, but the patient may not regain lost milestones or function.

Importantly, gene therapy using third-generation self-inactivating lentiviral vectors and autologous HCT has entered the clinical arena both for immunodeficiency diseases as well as metabolic disorders where the transformed cells cause sustained release of biotherapeutics. These include the European Medical Agency (EMA)-approved agent Strimvelis for ADA deficiency and the FDA-approved gene therapy onasemnogene abeparvovec-xioi (Zolgensma) for spinal muscular atrophy.

Autoimmune diseases

Autologous HCT has been used in multiple sclerosis, systemic sclerosis, rheumatoid arthritis, juvenile idiopathic arthritis, systemic lupus erythematosus, dermatomyositis/polymyositis, Crohn's disease, and autoimmune cytopenias with a randomized study in diffuse systemic sclerosis showing an EFS (74% versus 47%) and OS (86% versus 51%) benefit to autologous HCT compared to monthly cyclophosphamide. The therapeutic rationale for these transplantations is that high-dose chemotherapy may eradicate or modulate clones of autoreactive T cells. Allogeneic HCT has considerable treatment-related morbidity and mortality in this population and is not typically used outside of a clinical trial. The waxing and waning course of autoimmune disorders makes it difficult to define end points in these diseases. Nonetheless, patients with aggressive autoimmune disorders should consider clinical trials and examine this approach as one of their treatment options.

Hemoglobinopathies

Thalassemia major

The clinical manifestations of thalassemia are largely linked to sequelae of chronic anemia, ineffective erythropoiesis, and peripheral hemolysis. Allogeneic transplantation as a curative approach for this disease was pioneered in the 1990s by a team in Pesaro, Italy. Three factors predicted adverse transplantation outcomes: hepatomegaly (>2 cm below the costal margin), hepatic fibrosis, and irregular chelation. Disease-free survival exceeding 90% has been reported with favorable risk profile and matched sibling donors. For those lacking sibling donors, unrelated, haploidentical, and cord blood donor transplantations have shown promising results in both pediatric and adult patients. Patients with thalassemia major frequently develop mixed chimerism following transplantation, which often leads to marked improvement in their transfusion requirements. The patients remain at risk for graft rejection, however, especially those with persistence of >25% host cells

The major breakthrough in this disease has been the development of gene therapy, whereby transfusion-dependent patients over age 12 with $ß^0$ or severe $ß^+$ mutations and lacking a MRD were infused with cells transduced ex vivo with a lentiviral vector encoding the globin gene following MAC. Several vectors and gene therapy approaches have been examined. One trial used intraosseous infusion of cells while another vector encoded HbA with a T87Q amino acid substitution, a hemoglobin variant that resists sickling. The endopoints attained include transfusion independence in a sizable subset and reduce requirement in others. The EMA has conditionally approved betibeglogene autotemcel for the treatment of thalassemia major. The cost of these therapies remains a major barrier limiting access given the geographic distribution of these disease in middle- and lower-income countries.

Sickle cell disease

Between 1986 and 2013, more than 1000 patients received an HLA-identical sibling HCT and >90% were cured of sickle cell disease. Allogeneic transplantation and gene therapy offer the promise of cure to a subset of patients

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022

with sickle cell disease with severe clinical manifestations, including frequent pain crises, acute chest syndrome, and stroke or cerebrovascular disease requiring chronic transfusions. Transplant morbidity and mortality increases significantly starting in early adolescence and should generally be undertaken at centers with clinical experience with this unique subset of patients.

Recent data for 122 adults from 3 institutions undergoing MRD transplant using nonmyeloablative conditioning with alemtuzumab and 300 cGy of TBI is encouraging with overall and sickle-free survival at 1 and 5 years of 93% and 85% respectively. Successful allogeneic HCT appears to improve hemoglobin, hemolytic parameters, and hepatic iron levels while pulmonary function testing, hepatic histology, and neurovascular imaging remained stable, suggesting cessation of further sickle-related injury. Importantly, quality of life measures improved significantly following transplant. Clinical experience using donors other than matched siblings is increasing and offers an important solution to the bottle neck of matched sibling donor availability of <20%.

Simultaneously, multiple gene therapy strategies are in clinical trials with preliminary data showing their success without the morbidity and mortality of GVHD and no reported rejection. A gene editing approach using CRISPR-Cas9 to target *BCL11* as part of an autologous transplant to increase expression of fetal hemoglobin showed success in a proof-of-concept trial encompassing 1 patient with thalassemia major and another with sickle cell disease. However, clonal myeloid disease has emerged in recipients of the gene-edited cells after busulfan conditioning, emphasizing the need for ongoing study before broad adaptation. The choice of transplant versus gene editing will be one that is guided by emerging data on efficacy, access, as well as short- and long-term morbidity.

Solid tumors

Germ cell tumors

Approximately 15% to 20% of patients with multiply relapsed or overtly cisplatin-refractory germ cell tumors can be cured with high-dose carboplatin and etoposide followed by autologous HCT. In a large retrospective study, progressive disease before transplantation, primary mediastinal tumor, refractoriness to conventional-dose cisplatin, and human chorionic gonadotropin levels >1000 IU/L before transplantation predicted transplantation failure. The estimated 2-year survival rates were 51% and 5% for patients with no risk factors and multiple risk factors, respectively. This is an area where tandem transplant retains a therapeutic niche as demonstrated by a large retrospective experience of 445 metastatic germ cell tumor patients evaluating high-dose chemotherapy and tandem autologous stem cell transplant showing similar outcomes between patients over and under 40 years old. Over 80% of patients were able to receive both planned transplants; 2-year PFS was >55% and OS >60%.

Pediatric solid tumors

Many pediatric solid tumors demonstrate exquisite chemosensitivity, leading to the exploration of autologous HCT as a method of dose intensification for children presenting with high-risk or recurrent disease. The major examples are high-risk neuroblastoma (defined as age >1 year, metastatic disease, amplification of MYC oncogene, and histologic findings) and Ewing sarcoma with high-risk features at diagnosis, including large primary tumor size, pelvic location, and presence of overt metastatic disease.

Health inequities in transplantation

A CIBMTR analysis of more than 200,000 patients with leukemia, lymphoma, and myeloma from 1997 to 2002 showed a significantly higher odds ratio for receiving HCT in White compared to Black patients, with ORs of 1.24 for auto-HCT, 1.59 for HLA-identical sibling HCT, and 2.02 for unrelated donor HCT ($P < 0.0001$ for all comparisons). There has been longstanding recognition that the donor pool in national bone marrow registries disproportionately disadvantages non-White communities. The National Marrow Donor Program/Be The Match showed after analyzing more than 10 million unrelated donors, the probability of identifying a MUD was 75% for a White patient compared to 19% for a Black patient. Registry modeling has shown that simply increasing the number of minority volunteer donors cannot completely close the access gap. Incorporating posttransplant cyclophosphamide has liberalized the degree of permitted HLA mismatch and there is now widespread use of haploidentical donors. A recent phase 2 study showed this approach also improved outcomes for mismatched unrelated donors. Cord blood transplants are also used, albeit at select centers with expertise in this area.

Social determinants of health strongly affect access to and outcomes of allogeneic transplant through a diverse set of mechanisms. The importance of nonbiologic factors in transplant access is reflected in the extension of this disparity to autologous transplant. Because of the expensive and multidisciplinary nature of the procedure, socioeconomic status, health insurance, and health literacy factors may be directly relevant in contributing to racial disparities. Other barriers include comorbidities, availability of caregivers and transportation, as well as patient adherence to medications

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022

and outpatient follow-up care. A recent study drew attention to the importance of patients' community health status in predicting NRM following allogeneic HCT. Sociodemographic, environmental, and community indicators were aggregated to compute a community risk score that was strongly predictive of survival outcomes following transplant. These data suggest that disparities persist even after surmounting the barrier of identifying a donor and meeting eligibility criteria for transplant.

In addition to race, age remains an important barrier to transplant based on a recent meta-analysis. Strategies to make transplant more accessible to elderly patients include prospective and/or randomized controlled trials investigating HCT in this population such as the BMT CTN CHARM study that aims to validate pre-HCT factors (patient-reported factors, clinical factors, and biomarkers) and to risk stratify for NRM after allogeneic HCT in older adults . In addition, physician education and incorporation of geriatric assessments in transplant evaluations will help to increase transplant rates in this vulnerable population that often presents with high-risk disease.

Economics of hematopoietic cell transplantation

The cost of an HCT ranges broadly from $36,000 to $88,000 (US) for an autologous transplantation, to $200,000 (US) or more for a myeloablative allogeneic procedure. Intensity of conditioning, donor selection, pediatric age group, and posttransplant complications such as infections and GVHD, have been shown to be significant cost drivers. Early use of allogeneic HCT for sickle cell disease has been shown to improve health-related quality of life and reduced health care use over time in children and severely affected adults. Autologous transplant for autoimmune diseases has the benefit of a single procedure to provide self-tolerance rather than chronic immunosuppression. A recent analysis of more than 2000 procedures from 2010 to 2015 by the EBMT showed that autologous transplant use and outcomes for autoimmune diseases were correlated with the Human Development Index, health care expenditure, and team density (ie, the number of transplant teams divided by population) suggesting a need for centers of excellence. Formal health economic modeling is warranted to fully evaluate the cost-effectiveness of HCT versus the standard of care in autoimmune diseases. Existing frameworks such as the Institute for Clinical and Economic Review (ICER) help guide an understanding of financial value considerations. A recent report from ICER showed that while the cost-effectiveness of 2 FDA-approved CAR T therapies (tisagenlecleucel and axicabtagene ciloleucel) fell below or within commonly cited thresholds of $50,000 to $150,000 per quality-adjusted life year, changes will be needed in future pricing, payment, and delivery mechanisms to ensure patient access without threatening health system affordability.

Summary

The field of HCT and cellular therapy is rapidly evolving. Results have improved over the past decades and indications for HCT/CT continue to expand and change. Transplantation is more widely applicable because of improvements in supportive care and donor selection and the advent of reduced-intensity conditioning regimens. Adoptive cell therapy targeting cancer-associated antigens has added a powerful new treatment to existing therapies for patients with hematologic malignancies and soon may be applicable in solid tumors as well.

Bibliography

History

Appelbaum FR. Hematopoietic stem cell transplantation at 50. *N Engl J Med*. 2007;357(15):1472-1475.

Barnes DWH, Corp MJ, Loutit JF, Neal FE. Treatment of murine leukaemia with X-rays and homologous bone marrow. *BMJ*. 1956;ii:626-627.

Becker AJ, McCulloch EA, Till JE. Cytological demonstration of the clonal nature of spleen colonies derived from transplanted mouse marrow cells. *Nature*. 1963;197(4866):452-454.

Mathé G, Amiel JL, Schwarzenberg L, Catton A, Schneider M. Adoptive immunotherapy of acute leukemia: experimental and clinical results. *Cancer Res*. 1965;25:1525-1531.

McGovern JJ Jr, Russell PS, Atkins L, et al. Treatment of terminal leukemic relapse by total-body irradiation and intravenous infusion of stored autologous bone marrow obtained during remission. *N Engl J Med*. 1959;260(14):675-683.

Thomas ED, Buckner CD, Clift RA, et al. Marrow transplantation for acute nonlymphoblastic leukemia in first remission. *N Engl J Med*. 1979;301(11):597-599.

Thomas ED, Lochte HL Jr, Cannon JH, Sahler OD, Ferrebee JW. Supralethal whole body irradiation and isologous marrow transplantation in man. *J Clin Invest*. 1959;38(10 pt 1-2):1709-1716.

Thomas ED, Lochte HL Jr, Lu WC, Ferrebee JW. Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy. *N Engl J Med*. 1957;257(11):491-496.

Autologous transplantation

Barlogie B, Hall R, Zander A, Dicke K, Alexanian R. High-dose melphalan with autologous bone marrow transplantation for multiple myeloma. *Blood*. 1986;67(5):1298-1301.

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavrillaki on 10 December 2022

Buckner CD. Autologous bone marrow transplants to hematopoietic stem cell support with peripheral blood stem cells: a historical perspective. *J Hematother*. 1999;8(3):233-236.

Mobilization of PBSCs

Bensinger W, Appelbaum F, Rowley S, et al. Factors that influence collection and engraftment of autologous peripheral blood stem cells. *J Clin Oncol*. 1995;13(10):2547-2555.

DiPersio JF, Stadtmauer EA, Nademanee A, et al. Plerixafor and G-CSF versus placebo and GCSF to mobilize hematopoietic stem cells for autologous stem cell transplantation in patients with multiple myeloma. *Blood*. 2009;113(23):5720-5726.

Giralt S, Costa L, Schriber J, et al. Optimizing autologous stem cell mobilization strategies to improve patient outcomes: consensus guidelines and recommendations. *Biol Blood Marrow Transplant*. 2014;20(3):295-308.

Hopman RK, DiPersio JF. Advances in stem cell mobilization. *Blood Rev*. 2014;28(1):31-40.

Petit I, Szyper-Kravitz M, Nagler A, et al. Erratum: G-CSF induces stem cell mobilization by decreasing bone marrow SDF-1 and up-regulating CXCR4. *Nat Immunol*. 2002;3(7):687-694.

Sheppard D, Bredeson C, Allan D, Tay J. Systematic review of randomized controlled trials of hematopoietic stem cell mobilization strategies for autologous transplantation for hematologic malignancies. *Biol Blood Marrow Transplant*. 2012;18(8):1191-1203.

Siena S, Bregni M, Brando B, et al. Circulation of CD34+ hematopoietic stem cells in the peripheral blood of high-dose cyclophosphamide-treated patients: enhancement by intravenous recombinant human granulocyte-macrophage colony-stimulating factor. *Blood*. 1989;74:1905-1914.

HPC modifications

Frangoul H, Altshuler D, Cappellini MD, et al. CRISPR-Cas9 gene editing for sickle cell disease and β-thalassemia. *NEJM*. 2021;384(3):252-260.

Xu L, Wang J, Liu Y, et al. CRISPR-edited stem cells in a patient with HIV and acute lymphoblastic leukemia. *NEJM*. 2019;381(13):1240-1247.

Allogeneic transplantation and donor selection

Boudreau JE, Giglio F, Gooley TA, et al. KIR3DL1/HL A-B subtypes govern acute myelogenous leukemia relapse after hematopoietic cell transplantation. *J Clin Oncol*. 2017;35(20):2268-2278.

Brunstein CG, Eapen M, Ahn KW, et al. Reduced-intensity conditioning transplantation in acute leukemia: the effect of source of unrelated donor stem cells on outcomes. *Blood*. 2012;119(23):5591-5598.

Ciurea SO, Thall PF, Wang X, et al. Donor-specific anti-HLA Abs and graft failure in matched unrelated donor hematopoietic stem cell transplantation. *Blood*. 2011;118(22):5957-5964.

Eapen M, Rocha V, Sanz G, et al. Effect of graft source on unrelated donor haemopoietic stem-cell transplantation in adults with acute leukaemia: a retrospective analysis. *Lancet Oncol*. 2010;11(7):653-660.

Flomenberg N, Baxter-Lowe LA, Confer D. Impact of HLA class I and class II high-resolution matching on outcomes of unrelated donor bone marrow transplantation: HLA-C mismatching is associated with a strong adverse effect on transplantation outcome. *Blood*. 2004;104(7):1923-1930.

Petersdorf EW, Hansen JA, Martin PJ, et al. Major-histocompatibility-complex class I alleles and antigens in hematopoietic-cell transplantation. *N Engl J Med*. 2001;345(25):1794-1800.

Petersdorf EW, Malkki M. Human leukocyte antigen matching in unrelated-donor hematopoietic cell transplantation. *Semin Hematol*. 2005;42(2):76-84.

Sierra J, Storer B, Hansen JA, et al. Transplantation of marrow cells from unrelated donors for treatment of high-risk acute leukemia: the effect of leukemic burden, donor HLA-matching, and marrow cell dose. *Blood*. 1997;89:4226-4235.

Storb R, Prentice RL, Thomas ED. Marrow transplantation for treatment of aplastic anemia. An analysis of factors associated with graft rejection. *N Engl J Med*. 1977;296(2):61-66.

Weiden P, Flournoy N, Thomas ED, et al. Antileukemic effect of graft-versus-host-disease in human recipients of allogeneic-marrow grafts. *N Engl J Med*. 1979;300:1068-1073.

Weisdorf D, Cooley S, Wang T, et al. KIR B donors improve the outcome for AML patients given reduced intensity conditioning and unrelated donor transplantation. *Blood Adv*. 2020;4(4):740-754.

Alternate donor transplantation

Aversa F, Terenzi A, Tabilio A, et al. Full haplotype-mismatched hematopoietic stem-cell transplantation: a phase II study in patients with acute leukemia at high risk of relapse. *J Clin Oncol*. 2005;23(15):3447-3454.

Ballen KK, Koreth J, Chen YBY-B, Dey BR, Spitzer TR. Selection of optimal alternative graft source: mismatched unrelated donor, umbilical cord blood, or haploidentical transplant. *Blood*. 2012;119(9):1972-1980.

Barker JN, Byam C, Scaradavou A. How I treat: the selection and acquisition of unrelated cord blood grafts. *Blood*. 2011;117(8):2332-2339.

Bashey A, Zhang X, Sizemore CA, et al. T-cell–replete HLA-haploidentical hematopoietic transplantation for hematologic malignancies using post-transplantation cyclophosphamide results in outcomes equivalent to those of contemporaneous HLA-matched related and unrelated donor transplantation. *J Clin Oncol*. 2013;31(10):1310-1316.

Broxmeyer HE, Douglas GW, Hangoc G, et al. Human umbilical cord blood as a potential source of transplantable hematopoietic stem/progenitor cells. *Proc Natl Acad Sci*. 1989;86(10):3828-3832.

Brunstein CG, Fuchs EJ, Carter SL, et al. Alternative donor transplantation after reduced intensity conditioning: results of parallel phase 2 trials using partially HLA-mismatched related bone marrow or unrelated double umbilical cord blood grafts. *Blood*. 2011;118(2):282-288.

Ciurea SO, Zhang MJ, Bacigalupo AA, et al. Haploidentical transplant with posttransplant cyclophosphamide vs matched unrelated donor transplant for acute myeloid leukemia. *Blood*. 2015;126(8):1033-1040.

Fuchs EJ, O'Donnell PV, Eapen M, et al. Double unrelated umbilical cord blood vs HLA-haploidentical bone marrow transplantation: the BMT CTN 1101 trial. *Blood*. 2021;137(3):420-428.

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022

Ganguly S, Ross DB, Panoskaltsis-Mortari A, et al. Donor CD4+ Foxp3+ regulatory T cells are necessary for posttransplantation cyclophosphamide-mediated protection against GVHD in mice. *Blood*. 2014;124(13):2131-2141.

Kanakry CG, Ganguly S, Zahurak M, et al. Aldehyde dehydrogenase expression drives human regulatory T cell resistance to posttransplantation cyclophosphamide. *Sci Transl Med*. 2013;5(211):211ra157.

Luznik L, O'Donnell PV, Symons HJ, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, post-transplantation cyclophosphamide. *Biol Blood Marrow Transplant*. 2008;14(6):641-650.

Mehta RS, Holtan SG, Wang T, et al. Composite GRFS and CRFS outcomes after adult alternative donor HCT. *J Clin Oncol*. 2020;38(18):2062-2076.

Michel G, Galambrun C, Sirvent A, et al. Single- vs double-unit cord blood transplantation for children and young adults with acute leukemia or myelodysplastic syndrome. *Blood*. 2016;127(26):3450-3457.

Mielcarek M, Furlong T, O'Donnell PV, et al. Post-transplantation cyclophosphamide for prevention of graft-versus-host disease after HLA-matched mobilized blood cell transplantation. *Blood*. 2016;127(11):1502-1508.

Rocha V, Labopin M, Sanz G, et al. Transplants of umbilical-cord blood or bone marrow from unrelated donors in adults with acute leukemia. *N Engl J Med*. 2004;351(22):2276-2285.

Wachsmuth LP, Patterson MT, Eckhaus MA, et al. Post-transplantation cyclophosphamide prevents graft-versus-host disease by inducing alloreactive T cell dysfunction and suppression. *J Clin Invest*. 2019;129(6):2357-2373.

Bone marrow versus mobilized peripheral blood

Anasetti C, Logan BR, Lee SJ, et al. Peripheral-blood stem cells versus bone marrow from unrelated donors. *N Engl J Med*. 2012;367(16):1487-1496.

Bacigalupo A, Socié G, Schrezenmeier H; Aplastic Anemia Working Party of the European Group for Blood and Marrow Transplantation (WPSAA-EBMT). Bone marrow versus peripheral blood as the stem cell source for sibling transplants in acquired aplastic anemia: survival advantage for bone marrow in all age groups. *Haematologica*. 2012;97(8):1142-1148.

Lee SJ, Logan B, Westervelt P, et al. Comparison of patient-reported outcomes in 5-year survivors who received bone marrow vs peripheral blood unrelated donor transplantation. *JAMA Oncol*. 2016;2(12):1583-1589.

Stem Cell Transplant Trialist Group. Allogeneic peripheral blood stem-cell compared with bone marrow transplantation in the management of hematologic malignancies: an individual patient data meta-analysis of nine randomized trials. *J Clin Oncol*. 2005;23(22):5074-5087.

Thomas ED, Storb R. Technique for human marrow grafting. *Blood*. 1970;36:507-515.

Matched related versus matched unrelated donor

Gupta V, Tallman MS, He W, et al. Comparable survival after HLA-well-matched unrelated or matched sibling donor transplantation for acute myeloid leukemia in first remission with unfavorable cytogenetics at diagnosis. *Blood*. 2010;116(11):1839-1848.

Kollman C, Spellman SR, Zhang MJ, et al. The effect of donor characteristics on survival after unrelated donor transplantation for hematologic malignancy. *Blood*. 2016;127(2):260-267.

Peters C, Schrappe M, von Stackelberg A, et al. Stem-cell transplantation in children with acute lymphoblastic leukemia: a prospective international multicenter trial comparing sibling donors with matched unrelated donors—the ALL-SCT-BFM-2003 trial. *J Clin Oncol*. 2015;33(11):1265-1274.

Rowley SD, Donato ML, Bhattacharyya P. Red blood cell-incompatible allogeneic hematopoietic progenitor cell transplantation. *Bone Marrow Transplant*. 2011;46(9):1167-1185.

Saber W, Opie S, Rizzo JD, et al. Outcomes after matched unrelated donor versus identical sibling hematopoietic cell transplantation in adults with acute myelogenous leukemia. *Blood*. 2012;119(17):3908-3916.

Stem cell transplant recipients

Armand P, Gibson C, Cutler C, et al. A disease risk index for patients undergoing allogeneic stem cell transplantation. *Blood*. 2012;120(4):905-913.

Muffly L, Pasquini MC, Martens M, et al. Increasing use of allogeneic hematopoietic cell transplantation in patients aged 70 years and older in the United States. *Blood*. 2017;130(9):1156-1164.

Shah NN, Ahn KW, Litovich C, et al. Outcomes of Medicare-age eligible NHL patients receiving RIC allogeneic transplantation: a CIBMTR analysis. *Blood Adv*. 2018;2(8):933-940.

Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood*. 2005;106(8):2912-2919.

Conditioning regimens

Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: working definitions. *Biol Blood Marrow Transplant*. 2009;15(12):1628-1633.

Luger SM, Ringdén O, Zhang MJ, et al. Similar outcomes using myeloablative versus reduced intensity regimens for allogeneic transplants for AML or MDS. *Bone Marrow Transplant*. 2012;47(2):203-211.

Scott BL, Pasquini MC, Logan BR, et al. Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. *J Clin Oncol*. 2017;35(11):1154-1161.

Sullivan KM, Goldmuntz EA, Keyes-Elstein LK, et al. Myeloablative autologous stem-cell transplantation for severe scleroderma. *N Engl J Med*. 2018;378:35-47.

Adoptive cell therapy

Benjamin R, Graham C, Yallop D, et al. Genome-edited, donor-derived allogeneic anti-CD19 chimeric antigen receptor T cells in paediatric and adult B-cell acute lymphoblastic leukaemia: results of two phase 1 studies. *Lancet*. 2020;396:1885-1894.

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022

Depil S, Duchateau P, Grupp SA, et al. 'Off-the-shelf' allogeneic CAR T cells: development and challenges. *Nat Rev Drug Discov*. 2020;19:185-199.

Fesnak AD, June CH, Levine BL. Engineered T cells: the promise and challenges of cancer immunotherapy. *Nat Rev Cancer*. 2016;16(9):566-581.

Lim WA, June CH. The principles of engineering immune cells to treat cancer. *Cell*. 2017;168(4):724-740.

Liu E, Marin D, Banerjee P, et al. Use of CAR-transduced natural killer cells in CD19-positive lymphoid tumors. *N Engl J Med*. 2020;382:545-553.

Kumar A, Watkins R, Vilgelm AE. Cell therapy with TILs: training and taming T cells to fight cancer. *Front Immunol*. 2021;12:690499.

Mehta RS, Randolph B, Daher M, Rezvani K. NK cell therapy for hematologic malignancies. *Int J Hematol*. 2018;107(3):262-270.

Park JH, Geyer MB, Brentjens RJ. CD19-targeted CAR T-cell therapeutics for hematologic malignancies: interpreting clinical outcomes to date. Blood. 2016;127(26):3312-3320.

Shah NN, Johnson BD, Schneider D, et al. Bispecific anti-CD20, anti-CD19 CAR T cells for relapsed B cell malignancies: a phase 1 dose escalation and expansion trial. *Nat Med*. 2020;26:1569-1575.

Shah NN, Maatman T, Hari P, Johnson B. Multi Targeted CAR-T Cell Therapies for B-Cell Malignancies. *Front Oncol*. 2019;9:146.

Smith M, Zakrzewski J, James S, Sadelain M. Posttransplant chimeric antigen receptor therapy. *Blood*. 2018;131(10):1045-1052.

Stem cell transplantation and cellular therapy complications

Anasetti C, Logan BR, Lee SJ, et al. Peripheral-blood stem cells versus bone marrow from unrelated donors. *N Engl J Med*. 2012;367:1487-1496.

Bacigalupo A, Chien J, Barisione G, Pavletic S. Late pulmonary complications after allogeneic hematopoietic stem cell transplantation: diagnosis, monitoring, prevention, and treatment. *Semin Hematol*. 2012;49(1):15-24.

Bollard CM, Heslop HE. T cells for viral infections after allogeneic hematopoietic stem cell transplant. *Blood*. 2016;127(26):3331-3340.

Ho VT, Cutler C, Carter S, et al. Blood and marrow transplant clinical trials network toxicity committee consensus summary: thrombotic microangiopathy after hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2005;11(8):571-575.

Jodele S, Dandoy CE, Myers KC, et al. New approaches in the diagnosis, pathophysiology, and treatment of pediatric hematopoietic stem cell transplantation-associated thrombotic microangiopathy. *Transfus Apher Sci*. 2016;54(2):181-190.

Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124:188-95.

Lee DW, Santomasso BD, Locke FL, et al. ASBMT consensus grading for cytokine release syndrome and neurological toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. 2018;25:625-638.

Lilleby K, Garcia P, Gooley T, et al. A prospective randomized study of cryotherapy during administration of high-dose melphalan to decrease the severity and duration of oral mucositis in patients with multiple myeloma undergoing autologous peripheral blood stem cell transplant. *Bone Marrow Transplant*. 2006;37:1031-1035.

McDonald GB. Hepatobiliary complications of hematopoietic cell transplantation, 40 years on. *Hepatology*. 2010;51(4):1450-1460.

Peled JU, Gomes ALC, Devlin SM, et al. Microbiota as predictor of mortality in allogeneic hematopoietic-cell transplantation. *N Engl J Med*. 2020;382(9):822-834.

Richardson P, Riches ML, Kernan NA, et al. Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure. *Blood*. 2016;127(13):1656-1665.

Roddie C, Peggs KS. Immunotherapy for transplantation-associated viral infections. *J Clin Investig*. 2017;127(7):2513-2522.

Sharma A, Bhatt NS, St Martin A, et al. Clinical characteristics and outcomes of COVID-19 in haematopoietic stem-cell transplantation recipients: an observational cohort study. *Lancet Haematol*. 2021;8(3):e185-e193.

Tichelli A, Rovó A, Gratwohl A. Late pulmonary, cardiovascular, and renal complications after hematopoietic stem cell transplantation and recommended screening practices. *Hematology (Am Soc Hematol Educ Program)*. 2008;2008(1):125-133.

Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective. *Biol Blood Marrow*. 2009;15(10):1143-1238.

Tuncer HH, Rana N, Milani C, Darko A, Al-Hasmi S. Gastrointestinal and hepatic complications of hematopoietic stem cell transplantation. *World J Gastroenterol*. 2012;18(16):1851-1860.

Graft-versus-host disease

Carpenter P. How I conduct a comprehensive chronic graft-versus-host disease assessment *Blood*. 2011;118:2679-2687.

Ferrara JL, Levine JE, Reddy P, Holler E. Graft-vs-host-disease. *Lancet*. 2009;373(9674):1550-1561.

Filipovich AH. Diagnosis and manifestations of chronic graft-versus-host disease. *Best Pract Res Clin Haematol*. 2008;21(2):251-257.

Harris AC, Young R, Devine S, et al. International, multicenter standardization of acute graft-versus-host disease clinical data collection: a report from the Mount Sinai Acute GVHD International Consortium. *Biol Blood Marrow Transplant*. 2016;22(1):4-10.

Jagasia MH, Greinix HT, Arora M, et al. National Institute of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease. I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant*. 2015;21(3):389-401.

Jagasia M, Perales MA, Schroeder MA, et al. Ruxolitinib for the treatment of steroid-refractory acute GVHD (REACH1): a multicenter, open-label, phase 2 trial. *Blood*. 2020;135(20):1739-1749.

Joseph RW, Couriel DR, Komanduri KV. Chronic graft-versus-host disease after allogeneic stem cell transplantation: challenges in prevention, science, and supportive care. *J Support Oncol*. 2008;6:361-372.

Martin PJ, Rizzo JD, Wingard JR, et al. First- and second-line systemic treatment of acute graft-versus host disease: recommendations

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022

of the American Society of Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2012;18(8):1150-1163.

Pidala J, Hamadani M, Dawson P, et al. Randomized multicenter trial of sirolimus vs prednisone as initial therapy for standard-risk acute GVHD: the BMT CTN 1501 trial. *Blood*. 2020;135(2):97-107.

Zeiser R, von Bubnoff N, Butler J, et al; REACH2 Trial Group. Ruxolitinib for glucocorticoid-refractory acute graft-versus-host disease. *N Engl J Med*. 2020;382(19):1800-1810.

Late effects

El-Jawahri A, Traeger L, Greer JA, et al. Effect of inpatient palliative care during hematopoietic stem-cell transplant on psychological distress 6 months after transplant: results of a randomized clinical trial. *J Clin Oncol*. 2017;35(32):3714-3721.

Landgren O, Gilbert ES, Rizzo JD, et al. Risk factors for lymphoproliferative disorders after allogeneic hematopoietic cell transplantation. *Blood*. 2009;113(20):4992-5001.

Rizzo JD, Wingard JR, Tichelli A, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation: joint recommendations of the European Group for Blood and Marrow Transplantation, the Center for International Blood and Marrow Transplant Research, and the American Society of Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2006;12(2):138-151.

Relapse and maintenance

Horowitz MM, Gale RP, Sondel PM, et al. Graft-versus-leukemia reactions after bone marrow transplantation. *Blood*. 1990;75:555-562.

Le Gouill S, Thieblemont C, Oberic L, et al. Rituximab after autologous stem-cell transplantation in mantle-cell lymphoma. *NEJM*. 2017;377(13):1250-1260.

Lee CJ, Savani BN, Mohty M, et al. Post-remission strategies for the prevention of relapse following allogeneic hematopoietic cell transplantation for high-risk acute myeloid leukemia: expert review from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. *BMT*. 2019;54(4):519-530.

Schmid C, Labopin M, Nagler A, et al. Donor lymphocyte infusion in the treatment of first hematological relapse after allogeneic stem-cell transplantation in adults with acute myeloid leukemia: a retrospective risk factors analysis and comparison with other strategies by the EBMT Acute Leukemia Working Party. *J Clin Oncol*. 2007;25(31):4938-4945.

Acute leukemias (AML and ALL)

Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129(4):424-447.

Frey NV, Shaw PA, Hexner EO, et al. Optimizing chimeric antigen receptor T-cell therapy for adults with acute lymphoblastic leukemia. *J Clin Oncol*. 2020;38:415-422.

Goldstone AH, Richards SM, Lazarus HM, et al. In adults with standard-risk ALL, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). *Blood*. 2008;111(4):1827-1833.

Gupta V, Richards S, Rowe J, et al. Allogeneic, but not autologous, hematopoietic cell transplantation improves survival only among younger adults with acute lymphoblastic leukemia in first remission: an individual patient data meta-analysis. *Blood*. 2013;121(2):339-350.

Gust J, Hay KA, Hanafi L-A, et al. Endothelial activation and blood–brain barrier disruption in neurotoxicity after adoptive immunotherapy with CD19 CAR-T cells. *Cancer Discov*. 2017;7:1404-1419.

Holter Chakrabarty JL, Rubinger M, Le-Rademacher J, et al. Autologous is superior to allogeneic hematopoietic cell transplantation for acute promyelocytic leukemia in second complete remission. *Biol Blood Marrow Transplant*. 2014;20(7):1021-1025.

Jongen-Lavrencic M, Grob T, Hanekamp D, et al. Molecular minimal residual disease in acute myeloid leukemia. *N Engl J Med*. 2018;378(13):1189-1199.

Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med*. 2018;378:439-448.

Park JH, Rivière I, Gonen M, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. *N Engl J Med*. 2018;378:449-459.

Pasquini MC, Le-Rademacher J, Zhu X, et al. Intravenous busulfan-based myeloablative conditioning regimens prior to hematopoietic cell transplantation for hematologic malignancies. *Biol Blood Marrow Transplant*. 2016;22(8):1424-1430.

Ravandi F, Othus M, O'Brien SM, et al. US intergroup study of chemotherapy plus dasatinib and allogeneic stem cell transplant in Philadelphia chromosome positive ALL. *Blood Adv*. 2016;1(3):250-259.

Schuurhuis GJ, Heuser M, Freeman S, et al. Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party. *Blood*. 2018;131(12):1275-91.

Shah BD, Ghobadi A, Oluwole OO, et al. KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study. *Lancet*. 2021;398:491-502.

Spiegel JY, Patel S, Muffly L, et al. CAR T cells with dual targeting of CD19 and CD22 in adult patients with recurrent or refractory B cell malignancies: a phase 1 trial. *Nat Med*. 2021;27:1419-1431.

Venditti A, Piciocchi A, Candoni A, et al. GIMEMA AML1310 trial of risk-adapted, MRD-directed therapy for young adults with newly diagnosed acute myeloid leukemia. *Blood*. 2019;134(12):935-945.

Chronic leukemias (CML and CLL)

Craddock CF. We do still transplant CML, don't we? Hematology. 2018;2018(1):177-184.

Frey NV, Gill S, Hexner EO, et al. Long-term outcomes from a randomized dose optimization study of chimeric antigen receptor modified T cells in relapsed chronic lymphocytic leukemia. *J Clin Oncol*. 2020;38(25):2862-2871.

Kharfan-Dabaja MA, Kumar A, Hamadani M, et al. Clinical practice recommendations for use of allogeneic hematopoietic cell transplantation in chronic lymphocytic leukemia on behalf of the Guidelines

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022

Committee of the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2016;22(12):2117-2125.

Krämer I, Stilgenbauer S, Dietrich S, et al. Allogeneic hematopoietic cell transplantation for high-risk CLL: 10-year follow-up of the GCLLSG CLL3X trial. *Blood*. 2017;130(12):1477-1480.

Smith G, Apperley J, Milojkovic D, et al. A British Society for Haematology guideline on the diagnosis and management of chronic myeloid leukaemia. *Br J Haematol*. 2020;191(2):171-193.

Myelodysplastic syndromes

Bejar R, Stevenson K, Abdel-Wahab O, et al. Clinical effect of point mutations in myelodysplastic syndromes. *N Engl J Med*. 2011;364(26):2496-2506.

Della Porta MG, Jackson CH, Alessandrino EP, et al. Decision analysis of allogeneic hematopoietic stem cell transplantation for patients with myelodysplastic syndrome stratified according to the revised International Prognostic Scoring System. *Leukemia*. 2017;31(11):2449-2457.

de Witte T, Bowen D, Robin M, et al. Allogeneic hematopoietic stem cell transplantation for MDS and CMML: recommendations from an international expert panel. *Blood*. 2017;129(13):1753-1762.

Rio-Machin A, Vulliamy T, Hug N, et al. The complex genetic landscape of familial MDS and AML reveals pathogenic germline variants. *Nat Commun*. 2020;11(1):1044.

Lymphomas

Abeyakoon C, van der Weyden C, Harrop S, et al. Advances in frontline management of peripheral T-cell lymphoma. *Clin Lymphoma Myeloma Leuk*. 2021:S2152-2650(21)00020-3.

Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet*. 2020;396:839-852.

Bach PB, Giralt SA, Saltz LB. FDA approval of tisagenlecleucel: promise and complexities of a US$475 000 cancer drug. *JAMA*. 2017;318(19):1861-1862.

Brudno JN, Kochenderfer JN. Chimeric antigen receptor T-cell therapies for lymphoma. *Nat Rev Clin Oncol*. 2018;15(1):31-46.

Casulo C, Friedberg JW, Ahn KW, et al. Autologous Transplantation in Follicular Lymphoma with Early Therapy Failure: A National LymphoCare Study and Center for International Blood and Marrow Transplant Research Analysis. *Biol Blood Marrow Transplant*. 2018;24(6):1163-1171.

Chin CK, Lim KJ, Lewis K, et al. Autologous stem cell transplantation for untreated transformed indolent B-cell lymphoma in first remission: an international, multi-centre propensity-score-matched study. *Br J Haematol*. 2020;191(5):806-815.

Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood*. 2017;130(16):1800-1808.

d'Amore F, Relander T, Lauritzsen GF, et al. Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. *J Clin Oncol*. 2012;30(25):3093-3099.

Dreger P, Fenske TS, Montoto S. Cellular immunotherapy for refractory diffuse large B Cell lymphoma in the chimeric antigen receptor-engineered T cell era: still a role for allogeneic transplantation? *Biol Blood Marrow Transplant*. 2020;26(4):e77-e85.

Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol*. 2010;28(27):4184-4190.

Jacobson C, Chavez JC, Sehgal AR, et al. Primary analysis of Zuma-5: a phase 2 study of axicabtagene ciloleucel (axi-cel) in patients with relapsed/refractory (R/R) indolent non-Hodgkin lymphoma (iNHL). *Blood*. 2020;136(suppl 1):40-41.

Jurinovic V, Metzner B, Pfreundschuh M, et al. Autologous stem cell transplantation for patients with early progression of follicular lymphoma: a follow-up study of 2 randomized trials from the German Low-Grade Lymphoma Study Group. *Biol Blood Marrow Transplant*. 2018;24(6):1172-1179.

Kanate AS, Kumar A, Dreger P, et al. Maintenance therapies for Hodgkin and non-Hodgkin lymphomas after autologous transplantation: a consensus project of ASBMT, CIBMTR, and the Lymphoma Working Party of EBMT. *JAMA Oncol*. 2019;5(5):715-722.

Le Gouill S, Thieblemont C, Oberic L, et al; LYSA Group. Rituximab after autologous stem-cell transplantation in mantle-cell lymphoma. *N Engl J Med*. 2017;377(13):1250-1260.

Moskowitz CH, Nademanee A, Masszi T, et al; AETHERA Study Group. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2015;385(9980):1853-1862.

Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med*. 2017;377:2531-2544.

Osborne W, Marzolini M, Tholouli E, et al. Phase I Alexander study of AUTO3, the first CD19/22 dual targeting CAR T cell therapy, with pembrolizumab in patients with relapsed/refractory (r/r) DLBCL. *J Clin Oncol*. 2020;38:8001.

Ramos CA, Grover NS, Beaven AW, et al. Anti-CD30 CAR-T cell therapy in relapsed and refractory Hodgkin lymphoma. *J Clin Oncol*. 2020;38:3794-3804.

Sarina B, Castagna L, Farina L, et al. Allogeneic transplantation improves the overall and progression free survival of Hodgkin lymphoma patients relapsing after autologous transplantation: a retrospective study based on the time of HLA typing and donor availability. *Blood*. 2010;115(18):3671-3677.

Schmitz N, Pfistner B, Sextro M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. *Lancet*. 2002;359(9323):2065-2071.

Schuster SJ, Bishop MR, Tam CS, et al; JULIET Investigators. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med*. 2019;380(1):45-56.

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavrillaki on 10 December 2022

Stiff PJ , Unger JM, Cook JR, et al. Autologous transplantation as consolidation for aggressive non-Hodgkin's lymphoma. *N Engl J Med*. 2013;369(18):1681-1690.

Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. *N Engl J Med*. 2020;382:1331-1342.

Wang D, Zeng C, Xu B, et al. Anti-CD30 chimeric antigen receptor T cell therapy for relapsed/refractory CD30+ lymphoma patients. *Blood Cancer J*. 2020.10:8.

Plasma cell dyscrasias

Attal M, Harousseau JL, Facon T, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2003;349(26):2495-2502.

Attal M, Lauwers-Cances V, Hulin C, et al; IFM 2009 Study. Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. *N Engl J Med*. 2017;376(14):1311-1320.

Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012;366(19):1782-1791.

Knop S, Engelhardt M, Liebisch P, et al. Allogeneic transplantation in multiple myeloma: long-term follow-up and cytogenetic subgroup analysis. *Leukemia*. 2019;33:2710-2719.

Madduri D, Berdeja JG, Usmani SZ, et al. CARTITUDE-1: Phase 1b/2 study of ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T cell therapy, in relapsed/refractory multiple myeloma. *Blood*. 2020;136:22-25.

Moreau P, Kumar SK, San Miguel J, et al. Treatment of relapsed and refractory multiple myeloma: recommendations from the International Myeloma Working Group. *Lancet Oncol*. 2021;22(3):e105-e118.

Munshi NC, Anderson LD, Shah N, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. *N Engl J Med*. 2021;384:705-716.

Raje N, Berdeja J, Lin Y, et al. Anti-BCMA CAR T-cell therapy bb2121 in relapsed or refractory multiple myeloma. *N Engl J Med*. 2019;380:1726-1737.

Stadtmauer EA, Pasquini MC, Blackwell B, et al. Autologous transplantation, consolidation, and maintenance therapy in multiple myeloma: results of the BMT CTN 0702 trial. *J Clin Oncol*. 2019;37(7):589-597.

Benign hematologic diseases

Alzahrani M, Damlaj M, Jeffries N, et al. Non-myeloablative human leukocyte antigen-matched related donor transplantation in sickle cell disease: outcomes from three independent centres. *Br J Haematol*. 2021;192(4):761-768.

Eapen M, Brazauskas R, Walters MC, et al. Effect of donor type and conditioning regimen intensity on allogeneic transplantation outcomes in patients with sickle cell disease: a retrospective multicentre, cohort study. *Lancet Haematol*. 2019;6(11):e585-e596.

Frangoul H, Altshuler D, Cappellini MD, et al. CRISPR-Cas9 gene editing for sickle cell disease and β-thalassemia. *N Engl J Med*. 2021;384(3):252-260.

Iftikhar R, Chaudhry QUN, Anwer F, et al. Allogeneic hematopoietic stem cell transplantation in aplastic anemia: current indications and transplant strategies. *Blood Rev*. 2021;47:100772.

Leonard A, Tisdale J, Abraham A. Curative options for sickle cell disease: haploidentical stem cell transplantation or gene therapy? *Br J Haematol*. 2020;189(3):408-423.

Marktel S, Scaramuzza S, Cicalese MP, et al. Intrabone hematopoietic stem cell gene therapy for adult and pediatric patients affected by transfusion-dependent β-thalassemia. *Nat Med*. 2019;25(2):234-241.

Saraf SL, Oh AL, Patel PR, et al. Nonmyeloablative stem cell transplantation with alemtuzumab/low-dose irradiation to cure and improve the quality of life of adults with sickle cell disease. *Biol Blood Marrow Transplant*. 2016;22(3):441-448.

Taher AT, Musallam KM, Cappellini MD. β-Thalassemias. *N Engl J Med*. 2021;384(8):727-743.

Thompson AA, Walters MC, Kwiatkowski J, et al. Gene therapy in patients with transfusion-dependent β-thalassemia. *N Engl J Med*. 2018;378(16):1479-1493.

Tucci F, Scaramuzza S, Aiuti A, Mortellaro A. Update on clinical ex vivo hematopoietic stem cell gene therapy for inherited monogenic diseases. *Mol Ther*. 2021;29(2):489-504.

Solid tumors

Adra N, Abonour R, Althouse SK, et al. High-dose chemotherapy and autologous peripheral-blood stem-cell transplantation for relapsed metastatic germ cell tumors: the Indiana University experience. *J Clin Oncol*. 2017;35(10):1096-1102.

Agrawal V, Abonour R. Survival outcomes and toxicity in patients 40 years old or older with relapsed metastatic germ cell tumors treated with high-dose chemotherapy and peripheral blood stem cell transplantation. *Cancer*. 2021;127(20):3751-3760.

Health inequities in transplantation

Ailawadhi S, Parikh K, Abouzaid S, et al. Racial disparities in treatment patterns and outcomes among patients with multiple myeloma: a SEER-Medicare analysis. *Blood Adv*. 2019;3(20):2986-2994.

Barker JN, Boughan K, Dahi PB, et al. Racial disparities in access to HLA-matched unrelated donor transplants: a prospective 1312-patient analysis. *Blood Adv*. 2019;3(7):939-944.

Fiala MA, Wildes TM. Racial disparities in treatment use for multiple myeloma. *Cancer*. 2017;123(9):1590-1596.

Flannelly C, Tan BE, Tan JL, et al. Barriers to hematopoietic cell transplantation for adults in the United States: a systematic review with a focus on age. *Biol Blood Marrow Transplant*. 2020;26(12):2335-2345.

Gragert L, Eapen M, Williams EP, et al. HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry. *N Engl J Med*. 2014;371:339-348.

Hong S, Brazauskas R, Hebert KM, et al. Community health status and outcomes after allogeneic hematopoietic cell transplantation in the United States. *Cancer*. 2021;127(4):609-618.

Kirtane K, Lee SJ. Racial and ethnic disparities in hematologic malignancies. *Blood*. 2017;130(15):1699-1705.

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavrillaki on 10 December 2022

Majhail N, Nayyar S, Santibañez M, et al. Racial disparities in hematopoietic cell transplantation in the United States. *Bone Marrow Transplant*. 2012;47:1385-1390.

Shaw BE, Shaw AMJ, Burns L, et al. National Marrow Donor Program–sponsored multicenter, phase II trial of HLA-mismatched unrelated donor bone marrow transplantation using post-transplant cyclophosphamide. *J Clin Oncol*. 2021;39(18):1971-1982.

Economics of stem cell transplantation

Arnold SD, Brazauskas R, He N, et al. Clinical risks and healthcare utilization of hematopoietic cell transplantation for sickle cell disease in the USA using merged databases. *Haematologica*. 2017;102(11):1823-1832.

Majhail NS, Mothukuri JM, Brunstein CG, Weisdorf DJ. Costs of hematopoietic cell transplantation: comparison of umbilical cord blood and matched related donor transplantation and the impact of posttransplant complications. *Biol Blood Marrow Transplant*. 2009;15(5):564-573.

Saraf SL, Ghimire K, Patel P, et al. Improved health care utilization and costs in transplanted versus non-transplanted adults with sickle cell disease. *PLoS One*. 2020;15(2):e0229710.

Snowden JA, Badoglio M, Labopin M, et al. Evolution, trends, outcomes, and economics of hematopoietic stem cell transplantation in severe autoimmune diseases. *Blood Adv*. 2017;1(27):2742-2755.

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908677/chapter_14.pdf by Eleni Gavriilaki on 10 December 2022